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Vol. 226, No. 4 OCTOBER, 1953 No. 978

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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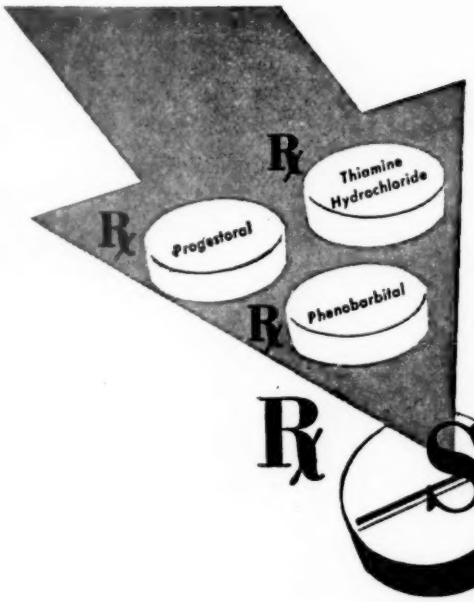

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1. Irvin, J. L.: The Secretion and Enterohepatic Circulation of Bile Acids: Replacement of Bile Acids in Biliary Insufficiency, North Carolina M. J. *13*:206 (April) 1952

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ORIGINAL ARTICLES

PENICILLIN REACTIONS: THEIR NATURE, GROWING IMPORTANCE, RECOGNITION, MANAGEMENT AND PREVENTION

By Richard A. Kern, M.D.
PROFESSOR OF MEDICINE

AND

Major Norris A. Wimberley, Jr., MC USA
RESIDENT IN MEDICINE

(From the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania)

The advent of penicillin in 1943, was hailed not only because of the remarkable therapeutic powers of that antibiotic, but also because of the infrequent and trifling reactions that followed its use. Today, it heads the list of medicinal agents in the frequency, diversity, and severity of the sensitivities which it induces. In current experience, it has replaced foreign sera as the commonest cause of fatal anaphylactic shock. It is responsible for a growing number of deaths due to irreversible vascular allergy, periarteritis nodosa. Yet, in many instances, sensitivity has unnecessarily been incurred. Moreover, the severest sensitivities can be recognized by skin tests (a rarity in the field of drug allergy). It is, therefore, our purpose to stress the growing need for preventing unnecessary sensitization, to describe the ways in which sensitivity manifests itself, to discuss the management of reactions, and the avoidance of the serious and fatal types.

HISTORICAL. Before the introduction of the sulfonamides in the mid-thirties, allergic reactions to medicaments were relatively uncommon. The majority were comparatively mild, and due most often to aspirin, quinine or ipecac, in the order mentioned. Severe reactions were rare and usually of the serum sickness variety; in isolated instances of anaphylactic, at times fatal, type, after the employment of the few foreign immune sera then in use. In the twenties, there was a flurry of cases of malignant neutropenia from antipyrin and related drugs that subsided when the manner of their causation was recognized.

The sulfonamides proved to be very potent sensitizers. Their use was followed by a sharp upswing in the severity of drug reactions, including fever, various skin eruptions, malignant neutropenia, purpura and hemolytic anemia. Their widespread use, in every trifling infection, resulted in great numbers of such cases. Often

enough, susceptible patients became sensitized to each new sulfonamide as it was exhibited in successive infections, and each sensitization was usually worse than its predecessor.

The introduction of penicillin was therefore the more welcome, since early reports had little or nothing to say about sensitivities (since they largely did not yet exist), and were optimistic as to possible untoward effects. Thus, in 1943, Florey and Florey[20], in their first 172 cases, observed no toxic symptoms "due to impurities". Lyons[35] reported urticaria as the commonest type of reaction, and suggested that some of these patients would probably not be troubled by future use of penicillin, since the reactions in some patients could be traced to a particular batch of the drug, while others reacted to every batch. Mahoney *et al.* in 1943[36], had little to say about allergic reactions in their extensive observations in syphilitics treated with penicillin.

Yet in the same year, Keefer *et al.*[28] in 500 patients, reported 7 with reactions characterized by fever, urticaria, chills, headache and generalized muscular pains, and a total of 14% had some degree of reaction after penicillin. More such observations, too numerous to cite here, were published in rapid succession. An excellent survey of this literature has been published under the title, "Penicillin Decade," by Smith and Walker[50].

The introduction and widespread use of antihistaminics served for a time, perhaps still does, to minimize the importance of penicillin sensitivity. First Benadryl, then Pyribenzamine, and later others were found to control the increasingly frequent, but still minor, types of reactions, notably itching and rashes, during penicillin therapy. It became rather general practice to continue the penicillin, in spite of such reactions, until the infection was cured and to use full doses of antihistaminics to control the side effects. It must be emphasized that these drugs are useless either to prevent, minimize or treat the severer reactions to penicillin.

A broadening spectrum of reactions producible by penicillin became apparent in numerous clinical reports. To cite only a few: Morris and Downing[38] in 1945, first noted bullous dermatitis with erythema and edema. Cormia *et al.*[7], reporting in that year on 2000 patients who had received prolonged penicillin therapy, recorded reactions of some type in 60.5%, including urticaria, angioedema, erythematovesicular eruptions, erythema nodosum, a serum sickness-like syndrome, Herxheimer reactions, shock, convulsions, psychotic depression, and after an *initial dose*, acute syncope with an anaphylactic type of reaction, in keeping with a severe atopic sensitivity. These authors stressed the severity of many of the reactions encountered. Duemling[12], who reported in 1946, on 17,879 Naval patients treated with penicillin, noted the occurrence of "Herxheimer" reactions in 10% of the 892 luetics in the group. Since urticaria, pruritus, and fever were the chief characteristics of these reactions, one must entertain the possibility that these were largely allergic in nature. Farrington and Tamura[15] in 1947, reported a case of exfoliative dermatitis due to penicillin. In the same year, Anderson[1] recorded a patient with joint swelling, toxic nephritis, anaphylactic purpura and melena after penicillin. Wright and Rule[61] in 1946, reported the first instance of local reactions in the mouth following the use of calcium penicillin lozenges. There have been many further observations of both local and distant reactions from such lozenges and troches.

Next, depot penicillins began to contribute more than their share, both in

numbers and in severity, of reactions. Penicillin in peanut oil and beeswax, introduced in 1944, produced many local reactions, including sterile abscesses that suggested an Arthus' phenomenon. Lepper *et al.*[34] in 1948, reported many more and severer reactions after the peanut oil-beeswax preparation than after procaine penicillin and fewest after aqueous penicillin. Haunz and Grinnell[23] in 1949, having used alternate doses of a peanut oil-beeswax preparation, and of procaine penicillin G with peanut oil, noted far more reactions, especially at the site of injection, after the former and, therefore, blamed the beeswax.

Here, again, one must reckon with several possibilities in the explanation of the causation of the reactions. Beeswax was undoubtedly a source of trouble, if only because of its variable and unpredictable composition. It was, therefore, very properly abandoned. The simultaneous injection of two substances, however, greatly increases the chance of sensitization to one that, given alone, may be a poor antigen. For example, it was shown by Woods[60] that a combination of lens protein and bacterial filtrate could induce sensitivity in an animal to the lens protein, when lens protein alone had failed. There is the further important fact that the preparation longest in use will provide more and severer reactions than will those recently introduced. As Smith and Walker[50] point out, in the early days of penicillin the sensitizing qualities of amorphous calcium penicillin, including the beeswax preparation, seemed to be greater than those of other penicillin salts. With the introduction of crystalline penicillin G, the reaction rate sharply dropped, only to rise again as more and more patients became sensitized during second, third or later courses. By the same token, any claims for low antigenicity of future preparations of penicillin should be withheld until supported by the experience of repeated use in the same patients.

Anaphylactic reactions constitute the most alarming and dangerous manifestation of penicillin sensitivity. The first was reported by Cormia *et al.*[7] in 1945. A year later, O'Donovan and Klorfajn[39] reported their patient in whom a foot infection in June, 1944, and a face infection in October, had been treated by a local penicillin spray, and in whom an intramuscular injection of penicillin in December, for recurrent infection, had caused severe anaphylactic shock. He was later desensitized by a 30-day injection procedure. Everett[14] in 1951, recorded two instances of anaphylactic reaction after the local use of penicillin in the maxillary antra.

ANAPHYLACTIC DEATHS. The first fatal reaction to penicillin was reported by Wilensky[59]. His patient, a man past 60, after gastrectomy, was given penicillin continuously for 5 days. When, on the fifth day, he developed vomiting, fever, and a rash, the penicillin was stopped, but he became steadily worse and died 3 days later. The report contains no record of previous allergic disease.

The second penicillin death was recorded by Walbott[56], in 1949. The patient, a woman of 39, with hay fever for 18 years, and severe asthma for 2 years, had previously received 3 courses of penicillin injections, and had experienced fever, hives, joint pains, and increased asthma, therefrom. The first intramuscular injection, of what was to have been the fourth course, was followed by anaphylactic shock and death in 3 hours.

Two deaths, then, had been reported throughout the world in 9 years of penicillin therapy: not an impressive record, considering the countless doses given in that time. Contrast this with the record of the next 18 months.

The third and fourth deaths were recorded by Curphy[10] in March 1952, both of them in asthmatics.

The fifth fatality was reported by Thomson[55] in July, 1952. This patient, a man of 67, had experienced a severe reaction after procaine penicillin, from which he had recovered. In the belief that this reaction had been caused by the procaine and not by the penicillin, the physician gave the patient an intramuscular injection of penicillin G. The patient was dead in 15 minutes. There was no record given of previous allergic disease.

The sixth death was reported by Higgens and Rothchild[24] in October, 1952. The patient, a 57-year-old man, had received penicillin, 2 years previously, after accidental lacerations. After the excision of a suspicious lump in the right breast, he was given an injection of procaine penicillin G, and within 2 minutes suffered an anaphylactic reaction that in spite of prompt measures, including positive pressure oxygen, atropine sulfate and aminophylline intravenously, and epinephrine into the heart, resulted in death 10 minutes later. It is pointed out that the patient had no infection, and that the lesion proved to be gynecomastia. There was no family or personal history of allergy.

The seventh death was reported by Mayer *et al.*[37] in January, 1953. The patient, a man of 47, had received 3 courses of penicillin without trouble, and in the course of an upper respiratory infection, he took a penicillin troche and promptly fainted, but recovered. Three months later, he was again given penicillin because of a persistently positive serological reaction, and promptly died in anaphylactic shock. There is no mention of other evidences of allergy in the patient. These authors, in the same report, recorded 5 instances of non-fatal anaphylactic reactions to penicillin.

The eighth death was reported by Siegal *et al.*[48] in January, 1953. The patient, a 67-year-old white woman, had had asthma for several years. She had been known to be allergic to various antigens, including aspirin. Because of recurrent respiratory infections, she had repeatedly been given penicillin. In an attack of asthma and tonsillitis, she was given an intramuscular injection of aqueous procaine penicillin. Within 30 seconds, an anaphylactic reaction began and in a few minutes she was dead. In the same report, the authors mentioned 2 "near-fatal" anaphylactic reactions, both in young physicians, and both with previous untoward experiences with penicillin. One was an asthmatic, and the other had mild perennial allergic rhinitis.

The ninth death was reported by Christenson *et al.*[6] in February, 1953. The patient, a 48-year-old sailor, with non-specific urethritis, promptly died after an injection of penicillin. A year and a half before, he had received penicillin in beeswax, and had used a penicillin ophthalmic ointment, without symptoms. He gave no history of other manifestations of allergy.

The tenth, eleventh, and twelfth deaths were reported by Stormont[52] in March, 1953. In a report, as Secretary of the Council on Pharmacy and Chemistry of the American Medical Association, he states that "in the past six months, fourteen severe anaphylactoid reactions, including three that resulted in death, have followed the administration of penethamate hydriodide (Neo-Penil)". He gave no clinical details in any of the cases.

The thirteenth, fourteenth, fifteenth, and sixteenth deaths were reported in May, 1953, by Feinberg *et al.*[18]. In the records of the Armed Forces Institute of Pathology, they found the following 4 previously unreported deaths from penicillin. The first was a 27-year-old

Negro male who died 20 minutes after an intramuscular injection of procaine penicillin in peanut oil with aluminum monostearate, given for a "cold" by a hospital corpsman. There was no previous history of allergy, and no previous record of administration of penicillin. No dates were given. The second was a 28-year-old white male who, in 1944, while under treatment for a shell wound of the elbow, was given intravenously, 100,000 units of penicillin in a liter of glucose and saline. He died 2 hours later. There was no previous history of penicillin therapy, and no history of other allergies. The third was a 23-year-old white nurse who, in December, 1950, gave herself a subcutaneous injection of 200,000 units of crystalline sodium penicillin G, and 2 minutes later developed anaphylactic symptoms, and died in 2 hours. Seven months previously, because of a cold with wheezing, she had received penicillin orally. A postmortem blood count showed 19% eosinophils and a total leukocyte count of 29,400. The fourth case was a 54-year-old white male who, in 1952, was given 800,000 units of penicillin for a cold. He was dead in 3 minutes. An asthmatic for 10 years, he had previously been given 20 injections of penicillin, the last dose 2 years before, without untoward effect. These authors also noted another fatal case in this group, but failed to mention that it had previously been reported by Christenson[6]. In their report, they also mention 4 non-fatal anaphylactic reactions, all in patients with obvious allergic disease. All 4 of these non-fatal patients gave strongly positive cutaneous tests with penicillin, when so studied after their penicillin reactions. Of the 4 patients, one was also found to react to the mold, *Penicillium*.

The seventeenth death is that of a previously unreported case, knowledge of which was obtained by one of us (R.A.K.) at a medical meeting in Toledo, in January, 1953. The patient, an adult male, was given an intramuscular injection of penicillin, in a doctor's office, because of an infection, and died there 3 minutes later. No further details were available.

Fifteen reported anaphylactic deaths in a year and a half emphasize the potential seriousness of penicillin sensitivity. In addition to deaths in anaphylactic shock, more protracted types of penicillin sensitivity have at times also proved fatal. Exfoliative dermatitis due to penicillin, chronic irreversible vascular lesions, including periarteritis nodosa, contribute additional deaths. Syphilitics have at times promptly died after penicillin induced Jarisch-Herxheimer reactions, in some of which a sensitization factor could have been involved. To get a complete estimate of the lethal seriousness of penicillin reactions, one would need to know not only how many anaphylactic deaths have not been reported, but in how many of the more protracted severe reactions, such as periarteritis nodosa and exfoliative dermatitis, the role of penicillin was not suspected. Penicillin sensitivity clearly deserves our respectful attention.

TYPES OF REACTION. A striking fact with regard to penicillin reactions is the multiplicity of forms in which they may occur. We therefore list those which have been reported, not necessarily in the order of their frequency, but rather according to the type of manifestation.

1. *Dermatitis medicamentosa.* This includes the commonest of the reactions, as first reported, and is still quite frequent. It consists of a variety of fleeting rashes, usually erythematous, punctate, or morbilliform in nature, and arising from both oral and parenteral administration.

2. *Urticaria* is a frequent manifestation. It may last a matter of hours or

days, or it may be greatly prolonged for from 3 to 15 months. It is quite probable, in the latter cases, that other allergens previously not of sufficient moment to cause symptoms themselves, manage to keep rolling the ball that penicillin started. Such chronic cases, as Epstein[13] pointed out, have a serious effect on the morale of the patient, and may lead to profound depression and thought of suicide.

3. Lesions like those of *erythema nodosum* and *erythema multiforme* are increasingly more frequent, since first reported by Cormia *et al.*[7].

4. *Contact dermatitis.* These lesions are the same as those of other contact eruptions, and vary in degree and extent with exposure. Contact dermatitis can result from the local use of penicillin, including sprays and ointments, and also from the handling of penicillin preparations by doctors and nurses.

5. *Exfoliative dermatitis.* An increasing number of exfoliative skin reactions to penicillin by any route of administration is being reported. The seriousness of such cases is emphasized by the fact that a fatal outcome has been reported in 3 instances. The patient of Rabinovitch and Snitkoff[42], was a 72-year-old woman that was given parenteral penicillin after an appendectomy. Skin reaction began 4 days after her discharge from the hospital, and ended in death 13 days after the onset. The allergic factor is further suggested by penicillin sensitivity in 2 of her children. Langdon's[33] fatal case was a 53-year-old man who was given intramuscular penicillin for a boil on the neck. His skin reaction began 4 days later, and was followed by evidences of renal shutdown and death on the fifteenth hospital day. Barksdale *et al.*[2] reported the case of a 52-year-old male who was given intramuscular penicillin in September, 1945, that was followed by a generalized rash. Two months later, he was given topical penicillin and a series of intramuscular injections. His condition grew rapidly worse, with an exfoliative and eventually bullous eruption, and he died 3 weeks later. The patient of Derzavis and Beinstein[11] had an exfoliative dermatitis that became hemorrhagic and gangrenous, but the patient fortunately recovered.

6. *Bullous dermatitis.* There have been reported additional cases in which diffuse bullous lesions have appeared soon after the administration of the drug and attended by severe systemic symptoms. In Berne's[3] patient who received penicillin in beeswax for pneumonia, the skin reaction appeared 2 days later, rapidly progressed with the appearance of bullae over the entire body, manifestations of shock, and death in 5 days.

7. *"Serum sickness" reaction.* This is now the commonest penicillin reaction, occurring, as Keefer[28] states, in 3% of all patients given penicillin orally or parenterally. The manifestations include pruritus and urticaria, joint pains, protracted irregular fever, and eosinophilia. Symptoms usually begin about a week after the administration of the drug, but may occur within 2 or 3 days or as late as 10 days after treatment. In these late cases, the cause of the reaction can be overlooked. It is pointed out that human serum sickness also comes on about a week or so after the injection of the foreign serum. It takes that long for body cells to become sensitized. The cells first sensitized react first with the foreign serum still present in the body (it takes 3 weeks for horse serum to be completely eliminated from the body). As additional cells become sensitized and react, the reaction has a crescendo course up to a point, and then slowly diminishes for another number of days. The "serum sickness" type of penicillin reaction has a similar mechanism and

picture, and it occurs oftenest, therefore, after depot penicillin. Just as serum sickness can at times be accelerated, depending on the timing of serum dosage, so comparable acceleration may occur after penicillin, usually with increased severity of reaction. The average duration of symptoms is 10 days, but may be prolonged to 8 weeks or more.

8. *Purpuric reactions.* These may occur alone, or in association with the severer exfoliative skin reactions, or with "serum sickness" reactions. Gross and microscopic hematuria may be present. At necropsy, similar lesions of the intestinal mucosa with ulceration have been found. In Criep and Cohen's[9] 3 patients, the platelet counts were normal, but it is reasonable to believe that, as in other allergic purpuras, an occasional case may show thrombocytopenia. Harkavy[22] has also reported 2 fatalities in patients with purpuric lesions, and extensive visceral manifestations due to penicillin reaction.

9. *Agranulocytosis*, a not uncommon manifestation of various drug sensitivities, has also been produced by penicillin. Spain and Clark[51] reported a patient, who was given penicillin before and after a cecostomy, in whom the leukocyte count fell from 13,000 to 2,800 on the second post-operative day, and to 100 on the next day with no neutrophils. The patient, during this time, had an erythematous macular rash. When penicillin was stopped the leukocyte count again rose to 10,000, but the patient succumbed.

10. *Photosensitivity.* This has been reported only once, (Canizares[5]).

11. *Lupus erythematosus disseminatus.* The question of a possible etiological role of penicillin in lupus erythematosus has been raised by several writers. Gold[21] reported 8 cases in whom he believed that penicillin could have been to blame. The evidence, however, was equivocal. More significant is the report of Walsh and Zimmerman[58], who studied 6 patients with penicillin reactions from this standpoint. Three had mild reactions; the other 3 had severe reactions, one with giant urticaria, purpura, and joint swelling, one with exfoliative dermatitis, and one with severe serum sickness-type of reaction. Each of the patients, with a severe reaction, was found to have L. E. cells in the bone marrow, and a demonstrable L. E. factor in the plasma. They properly suggest that the L. E. phenomenon may be related to hypersensitivity, as well as to lupus erythematosus disseminatus.

This further possibility may also exist: in some instances, allergy, and perhaps penicillin allergy, may be a factor in the etiology of lupus erythematosus disseminatus. However, it should be pointed out that this could be true in only a minority of cases of that disease which occurs so predominantly in women, whereas, allergy is equally distributed between the sexes.

12. *Periarteritis nodosa.* The earlier concept of human disease due to hypersensitivity, held that increased capillary permeability (edema), and smooth muscle spasm, were the basic phenomena of all allergic reactions. Such edema and smooth muscle spasm are wholly reversible: the urticarial wheal, the bronchial edema, and muscle spasm, leaves behind no trace of structural change, but this concept is no longer adequate. It is now known that there can be more severe and prolonged allergic reactions that produce organic destructive, irreversible lesions. The work of Rich and Gregory[44,45,46], is particularly signficant. Rich demonstrated in rabbits the production, by means of foreign serum injection, of necrotizing arterial and renal lesions indistinguishable from those of human periarteritis nodosa.

He found similar lesions in patients, after sulfonamide therapy, who had normal vessels on biopsy before treatment. The incidence of periarteritis nodosa increased twelvefold after the introduction of sulfonamides in 1935. That increase has not abated, since penicillin has largely replaced the sulfonamides. It is significant that a considerable percentage of patients with periarteritis nodosa are asthmatic. Rackemann and Greene[43] have suggested that when asthmatics develop an eosinophilia over 25%, and complain of pain in the extremities, one should think of the development of periarteritis nodosa. More recently, an occasional case of severe and prolonged penicillin reaction has gone on to necrotizing arterial damage with fatal outcome. Harkavy[22] has reported such cases, and one of us (R. A. K.) has seen 2 similar cases. They had apparently begun as "serum sickness" reactions that were prolonged over many weeks, and ended up as periarteritis nodosa.

13. *Anaphylaxis.* There is no need to give in detail the picture of anaphylactic shock as it occurs after penicillin administration. It differs in no way from anaphylactic shock induced by other causes. Three points should be emphasized: it can be precipitated by any preparation of penicillin, and by any route of administration. The sooner the reaction begins after the administration, the severer the reaction: fatal reactions rarely begin more than 15 minutes after the drug is given. Anaphylactic sensitivity is attended by circulating antibodies, and by an immediate whealing reaction on skin test, thereby furnishing the chief clue to the prevention of anaphylactic shock and death. This will be discussed further in this paper.

14. *Miscellaneous.* Convulsions have followed the intrathecal injection of penicillin: Talbot[54], in a review of the intrathecal effects of penicillin, has called attention to arachnoiditis, transverse myelopathy, headache, nausea, vomiting, convulsions, and unconsciousness. Felder and Felder[19] have recorded evidences of liver damage after penicillin in patients with urticarial reactions who showed abnormal liver function tests, but without jaundice. Kolb and Gray[30] have reported 7 cases of peripheral neuritis. There are a number of references to the occurrence of the so-called Jarisch-Herxheimer reaction after penicillin in patients with syphilis. There have also been reported evidences of severe hydroarthrosis, of albuminuria, and of protracted fever. Falk and Newcomer[16] reported 2 cases in which Loeffler's syndrome with fever, patchy bronchopneumonia, leukocytosis, and eosinophilia, occurred after injection of penicillin in oil and beeswax.

FACTORS FAVORING PENICILLIN SENSITIZATION. 1. *Sensitizing exposure.* It is highly significant that, in the overwhelming majority of patients who suffer any type of penicillin reaction, there is obtained a history of previous administration of the drug. Only rarely does a patient experience a reaction after the first dose. This fact helps to account for the observation that, when penicillin first came into use, reactions were relatively rare, since few, if any, patients had had previous penicillin treatment. Today, however, it is hard to find a patient who has not had penicillin. It is even difficult, in hospitals, to find patients who are not getting penicillin: in looking over ward patients, to serve as negative controls in immunologic studies, only 4 of 50 patients were not actually receiving penicillin at the time (March 1953). It seems further to be true that patients who have had repeated courses, and larger doses, show more frequent and severer reactions. As long ago as 1947, Pillsbury *et al.*[41] noted an incidence of urticaria in 1.8% of the first 824 cases

treated, whereas, of the 200 cases retreated, the incidence of urticaria was 6%.

2. *Allergic constitution.* It is a significant fact that of the 17 fatal cases of anaphylactic shock above noted, 5 were asthmatic. It is probable that several more of the other 12 may have had eczema in infancy, or allergic rhinitis, as evidence of their allergic nature. Since 15% of our population are of such major allergic constitution, it is clear that one in every 7 patients given penicillin is a candidate for eventual penicillin sensitivity.

3. *Penicillin preparation and route of administration.* It is known that any penicillin preparation, and any mode of administration, can precipitate a reaction in a sensitized person. It is probably true that any preparation, and any mode of administration, can induce sensitization, but perhaps in different degrees. *Oral* administration is probably less productive of sensitivity than is parenteral administration. *Local* applications, on the other hand, have been productive of considerable local sensitization, as Templeton *et al.*[53] early showed, and in addition, are of relatively little therapeutic value. Kutscher, and his dental associates[32], among others, have shown a similar excessive local sensitizing effect in the mouth when penicillin is given in lozenges and troches. We are convinced that depot penicillins induce sensitivity oftener, and more severely, than do other preparations. This may be due to at least 2 factors: a greater amount of sensitizing material that is longer present, and the possible synergistic effect when 2 substances are injected simultaneously.

That various preparations of penicillin may possess different degrees of antigenicity must be admitted. The recent experiences with a high percentage of sensitization and reaction after the use of "Neo-Penil" might be considered to support this view.

4. *Cross reactions with other fungi.* It has been suggested that sensitivity to related molds might be responsible for a cross sensitivity with penicillin, and might explain some of the reactions occurring after the first administration of the drug. Peck *et al.*[40] tested over 500 individuals with penicillin and trichophytin, and felt that the number of positive reactions by intracutaneous test (48-hour delayed reaction) to both substances was sufficient to suggest cross reaction. Cormia *et al.*[8], on the basis of studies in guinea pigs, concluded that there was a common antigen in penicillin, *tinea gypsum* and other pathogenic fungi. Feinberg[17] however, failed to find positive skin tests with penicillin in patients who reacted to various inhalant molds, including some forms of *Penicillium*. It must be pointed out, however, that cross reactions between biologically closely related proteins in patients sensitized to one of the group occur in only a minority of such cases, yet definitely oftener than to other unrelated substances. One of us (R. A. K.) has been definitely impressed by the greater frequency of a history of penicillin sensitivity in those who on routine testing gave a positive reaction to *Penicillium roqueforti*, an ingested mold.

THE NATURE OF PENICILLIN SENSITIVITY. It is customary in allergic theory and practice to classify the clinical manifestations of human hypersensitivity under certain major headings: anaphylaxis, atopy (familial allergy), and various types of acquired allergy including contact dermatitis, serum allergy, drug allergy, and bacterial allergy. The classification is, however, not absolute since there are various exceptions and overlappings. Thus, serum allergy and drug allergy may be either acquired or familial.

These several types of clinical allergy are attributed to different immunologic mechanisms. This is not the place to go into detail about the several types of antibodies that characterize these conditions. It may be said, however, that some of them are cellular, that is, fixed within the cells of the reacting tissues, and others are humoral, that is, present in circulating body fluids. Yet, the primary origin of the humoral antibodies is undoubtedly cellular. Most antigens tend to produce some one of the clinical types of allergy mentioned above, but there are many eruptions which, under some circumstances, the same antigen may induce in different patients, occasionally in the same patient, 2 or more of the types of clinical sensitization.

Penicillin appears to have an unusually broad spectrum of types of sensitivity which it can bring about. The numerous manifestations of penicillin sensitivity described above testify to this fact. It raises the question: are the different mechanisms above mentioned based entirely on differences in kind, or may some of them be differences only in degree? It is possible, for example, that when cellular antibodies are produced in overwhelming amounts that some will of necessity spill over into extracellular fluids and appear as humoral circulating antibodies. This is admittedly pure speculation.

In the great majority of cases of penicillin sensitivity, the antibodies are purely cellular. They are, therefore, demonstrable in the first place by patch test, as in cases of contact dermatitis. At times, they may also be demonstrated by the delayed or tuberculin type of reaction after intracutaneous testing.

In the severest types of penicillin sensitivity, that is, those which are clinically manifested by the anaphylactic shock reaction, circulating antibodies have usually been found. These may be demonstrated in 2 ways: first, the immediate whealing reaction (by cutaneous or intracutaneous technique and comparable to the usual skin reactions in pollinosis), and second, by the Prausnitz-Kustner reaction on passive transfer. There are no reports as yet as to the possible presence of precipitins in the blood of patients who experience an anaphylactic reaction to penicillin.

Great importance attaches to the presence of these circulating antibodies in the severest type of penicillin allergy, therefore, some confirming observations are cited. Templeton *et al.*[53] who studied 5 cases of penicillin urticaria were able to demonstrate positive skin test reactions in 20 minutes in sites passively sensitized in suitable recipients. Four control studies gave negative reactions. Waldo and Tyson[57] demonstrated circulating antibodies by passive transfer in certain cases of severe penicillin reaction. Mayer *et al.*[37] reported 4 positive passive transfer results in 5 patients who had recovered from severe anaphylactic penicillin reactions. In our patient who recovered from a near-fatal anaphylactic penicillin reaction, we were able to demonstrate circulating antibodies by passive transfer (details below).

Positive cutaneous immediate whealing reactions in patients with the anaphylactic type of penicillin sensitivity have been reported by Burleson[4], Siegal *et al.*[47], Simon[49], and others. We found it in our patient (here recorded).

DURATION OF SENSITIVITY. It is never possible to predict in any case of clinical manifestation of allergy, for example, asthma, hay fever, urticaria, eczema, penicillin sensitivity or any other allergic disease, how long that sensitivity will last. It is not even possible to give average figures for groups of conditions. At best, one may say that the milder types of sensitivity

are likely to clear up spontaneously in a matter of months or a year or two, and that the more severe the clinical allergic manifestations, the longer will it last, even a lifetime. Occasionally, mild allergic states can last a lifetime or may even become more severe, so that a patient who routinely has mild symptoms from exposure to a given antigen, may suffer fatal anaphylaxis on the very next exposure. These facts are common knowledge.

Yet it was stated by Lyons[35], in 1943, that if a patient has an urticarial reaction on one occasion, he will probably not have a similar reaction if penicillin is used again at a later date. Siegal[47], as recently as 1951, stated that penicillin is tolerated without incident by the great majority of patients who give a history of a single previous reaction to the drug, even though that reaction occurred only a few days or weeks previously. To follow such a principle would be courting disaster. In Thomson's patient (*loc. cit.*) who had recovered from one penicillin reaction, an intramuscular dose two months later proved promptly fatal. In the patient reported by Mayer *et al.* (*loc. cit.*) 3 courses of penicillin had been uneventful; then a penicillin troche caused a "queer feeling" in the chest and a brief fainting spell. Three months later, an injection of penicillin promptly killed him. In 1953, Siegal, with his associates[48], reported a death, and 2 near-fatalities in persons with previous minor reactions to the drug.

RECOGNITION OF PENICILLIN SENSITIVITY. 1. A routine history for personal or familial allergy should be taken in every patient who is a candidate for penicillin therapy. If the patient or a member of his family has had asthma, hay fever, eczema, hives, a reaction to any food or medicine, or of routinely sneezing 6 or more times in a row, that patient is a potential candidate for easier sensitization, and one should proceed with more care.

2. Every patient should be asked about previous administration of penicillin in any way. Anyone who has previously received penicillin must be suspected of possible penicillin sensitivity, the more so, in the presence of a positive personal or familial history of other allergy.

3. Conversely, one may be reasonably sure that a patient, who has never received penicillin, will not show the most dangerous or anaphylactic type of sensitivity upon first administration. It is even more certain that subsequent doses, in the same series of injections, will not cause severe reactions if the first dose did not produce a reaction, providing the interval between the doses of a series is not greater than 4 days. It is when intervals of 10 days or more have elapsed, that there has been time for anaphylactic sensitivity to develop.

4. Patients who have previously received penicillin should be carefully questioned about any reactions that may have resulted. Specifically, they should be asked about marked swelling and itching at the site of injection, local comparable manifestations in the mouth in case of the use of troches, acute gastric irritation after oral administration, or general reactions, including, rashes, cough, wheezing, angioedema, or fainting.

5. All patients who have previously received penicillin, and who give a personal or familial history of allergy, or a history of any reaction on previous penicillin administration, should be subjected to a cutaneous (scratch) test with penicillin. A drop of the preparation to be used, a fresh solution, is brought in contact with a superficial cut through the outer layer of the skin but not deep enough to draw blood. The site is observed for evidence of erythema and wheal formation within

20 minutes. The development of a wheal and erythema constitutes a positive test, and is indicative of a high degree of sensitivity with real danger of anaphylaxis. It would be dangerous to give penicillin to such a patient.

6. A patient who gives a negative cutaneous test may nevertheless be highly sensitive to penicillin, since the great majority of those sensitive to penicillin do not have circulating antibodies. Therefore, every patient with a personal or familial history of allergy or a history of previous reaction, be it ever so slight, to administered penicillin, should be subjected to an intracutaneous test, since their circulating antibodies may be inadequate for the less sensitive cutaneous technique to evoke a reaction. With a tuberculin syringe that has been sterilized by boiling, there is injected intracutaneously 0.02 cc. of a penicillin solution with 5000 units per cc. A positive reaction, with wheal and erythema in 20 minutes, indicates a dangerous degree of sensitivity, and the patient should not be given penicillin therapy. The immediate intracutaneous reaction may be negative, but may evoke a delayed reaction at the site of injection in 24 to 48 hours. Such patients may be given penicillin with much less danger of an anaphylactic reaction, but with the chance of some allergic response. It must be admitted that even anaphylactic shock, albeit not fatal, has occurred in those showing a delayed reaction, and severe exfoliative dermatitis has likewise resulted. Here one must weigh the gravity of the condition under treatment against the risk of reaction.

7. It should be emphasized that in patients suspected of marked sensitivity to penicillin, the *cutaneous* test should be performed before proceeding to the *intracutaneous* test. Mayer *et al.*[37] reported a constitutional reaction in a patient whose intracutaneous test dose was only 0.01 cc. of a penicillin solution with only 1000 units per cc.

8. In patients whose alleged reactions to previous penicillin were skin manifestations, it may be possible to discover such sensitivity by means of a patch test. In the usual manner, there is applied a penicillin solution with a strength of 50,000 units per cc. A positive reaction should be looked for after 24 to 48 hours.

9. *Interpretation of skin test results.* It must be admitted that there is as yet no complete agreement as to the value and significance of skin test results. In our opinion, the following statements are conservative and tenable: A positive test, early or late, by either cutaneous or intracutaneous technique, means that the use of penicillin will probably be followed by a reaction. If the skin reaction be of the early type, the more likely is that reaction to be an anaphylactic one. It is, unfortunately, true that the longer the interval between the patient receiving his sensitizing dose of penicillin, the less likely is the skin reaction to be an immediate positive reaction, (it may disappear in from 8 to 24 months) yet, the patient may still be systemically quite sensitive. Here, it is of some value that the delayed reaction will be found persisting longer. A negative patch test alone is no guarantee against reaction from injected penicillin.

PREVENTION OF SENSITIZATION TO PENICILLIN. 1. By far the commonest cause of unnecessary sensitization to penicillin is the routine use of that drug in every infection, even of the most trifling nature. Current practice seems to be to give penicillin for a few days, and then, if the temperature does not return to normal, to make a physical examination. All allergic individuals should be instructed to ask their physicians to avoid penicillin except in case of a serious disease. Yet,

all too often, they are given penicillin for a common cold, and then find themselves sensitive when the drug is really needed in a pneumonia or for a serious wound. This is, above all, the responsibility of the general practitioner: he must learn that it is folly to shoot sparrows with a 16-inch gun.

2. One should especially avoid the use of depot penicillin in those of allergic constitution.

3. Since the simultaneous injection of 2 foreign substances is more likely to induce sensitivity to one or both of them, one should avoid the use of penicillin in combination with other substances for parenteral administration.

4. Since penicillin induces sensitization oftenest when applied locally, less often when injected parenterally, and least often when given by mouth, the oral route should be given preference. This rule, again, is more applicable in the case of an allergic individual. The objection that oral dosage must be larger, and therefore, incurs unnecessary expense, is hardly valid today. It is true, as Krantz and Carr[31] point out, that orally administered penicillin is to a large extent destroyed by the gastric acid, so that the oral dose needs to be 5 to 6 times as great as the intramuscular dose. This may be offset to some degree by giving the penicillin between meals, and combined with a suitable buffer salt or antacid. But penicillin is now so cheap that it is less expensive to give a larger dose than to protect the medicament by giving it in "enteric coated" preparations. In 1944, the actual cost of the manufacture of penicillin was $19.00 per 100,000 units. Today, the wholesale price is 3.4 cents per 100,000 units. The local use of penicillin by troches, sprays, aerosols, and ointments should be discouraged.

THE PREVENTION OF PENICILLIN REACTIONS. 1. The best way to prevent a penicillin reaction, in a potentially or proven sensitive patient, is to give another drug. This drug is to be selected on the basis of demonstrated sensitivity of the organism involved in the infection concerned.

2. Attempts at hypo-allergic administration have been proposed. They consist in combining the penicillin with an antihistaminic in the same injection. Simon[49], using Decapryn Succinate with the penicillin, reported 2.4% of rashes and urticarial reactions, as opposed to 6.5% when the penicillin was given alone. It must be emphasized, however, that this applies only to the lesser types of penicillin sensitivity. The procedure is useless in the face of anaphylactic sensitivity.

3. Because absorption is slower from the digestive tract, *oral administration* will be followed by a lesser acute reaction than when the drug is given parenterally.

4. Keeney[29] pointed out that in sensitive patients who seriously needed penicillin to treat an existing disease, serious reaction to penicillin could be avoided by suitable pre-treatment and accompanying treatment with ACTH or cortisone.

TREATMENT OF PENICILLIN REACTIONS. 1. *Anaphylactic shock.* The management of anaphylactic shock is increasingly more difficult. The greater the sensitivity of the patient, the sooner the reaction begins after the dose of penicillin. In the records of the 17 fatal anaphylactic cases, when symptoms began within a minute or two and death came in 10 to 15 minutes, it was noted 5 times that all was over before any treatment could be given, and probably for the same reason, no mention of treatment was made in 5 others. In the rest, no significant effects had been achieved by the following measures: subcutaneous, intramuscular and even intracardiac epinephrine; parenteral nikethamide, ephedrine and Coramine; intravenous

calcium gluconate and aminophylline; and, administration of oxygen, by mask or positive pressure.

In the case reports of patients who recovered from anaphylactic shock, and in whom the reactions were less acute but nonetheless alarming, those in attendance usually stated that treatment had been effective. Yet, one patient is recorded as having recovered without treatment. The means used included epinephrine by hypodermic and intravenous drip; intravenous Benadryl; hypodermic caffeine sodium benzoate; artificial respiration, tripelennamine hydrochloride (Pyribenzamine), Benadryl, and aminophylline by mouth; various vasopressor drugs and oxygen. In our patient, we used ACTH by intravenous drip.

We believe that this record can be improved. a) The first requisite, as Hoagland[25] has emphasized, is preparedness to meet the emergency. This includes the availability of a tourniquet, sterile syringes and epinephrine, Benadryl or Pyribenzamine for parenteral use, other indicated drugs and oxygen.

b) When penicillin is given parenterally, it should be injected into the arm at a low enough level to make a tourniquet effective. At the first sign of a severe reaction, the tourniquet should be applied and kept in place, except at long intervals, to delay absorption (one might even be justified in making a crucial incision at the injection site and applying suction as recommended in snakebite).

c) The airway should be kept open and oxygen administered by mouth.

d) Sympathomimetic drugs should be given by intravenous drip, preferably epinephrine.

e) Antihistaminics may be given intravenously. Burleson[4] reported improvement within 10 minutes after intravenous Benadryl.

f) To prolong and hold the effect initiated by the preceding measures, ACTH may be given in intravenous drip or cortisone by mouth.

2. *Lesser reactions.*

a) Stop the penicillin.

b) Medication to be used depends upon the severity of the reaction.

c) For milder reactions, full doses of antihistaminics and ephedrine are indicated.

d. For exfoliative dermatitis, cortisone should be given beginning with 300 mg. in divided doses over the first 24 hours, 200 mg. the second day, 100 mg. daily for a week, and then 75, 50, and 25 mg. respectively on 3 subsequent days.

e) In case of periarteritis nodosa, cortisone in full dosage and over a protracted period is required.

3. The management of *chronic urticaria,* and of severe *"serum sickness"* reactions deserves special comment. The penicillin should be stopped and antihistaminic drugs given in full dosage. The diet should be restricted to cooked foods only, and in addition, the patient should eat no fish or sea food, no nuts and no chocolate. If symptoms are completely relieved, the antihistaminic drugs should be gradually tapered off; and if symptoms do not recur, the diet may be gradually relaxed. If symptoms are not relieved by antihistaminics, and the diet mentioned, then food sensitivities should be tested and the diet arranged accordingly. If no positive food reactions are found, then a course of cortisone, as mentioned under exfoliative dermatitis, should be given.

The following cases are presented to illustrate certain practical points in diagnosis and management.

Case Reports. CASE 1. W. McM., a white male, age 65, was brought to the accident ward of the hospital at 3:10 p.m., on January 30, 1953, in the midst of an anaphylactic reaction brought on by an intraluteal

injection of crystalline penicillin G less than an hour before. He had been asthmatic for many years, and also had chronic bronchial infection. His first contact with penicillin had occurred 4 years before, when an operation for rectal neoplasm had been performed. In December, 1952, there was an increase of cough and purulent sputum, for which he was given crystalline penicillin G by his family physician without reaction, and with clinical improvement. Late in January, 1953 symptoms again flared up, this time with fever, and because of this his physician again gave an injection of penicillin on the afternoon of January 30. Within 2 minutes, his face became flushed and livid, and breathing was labored. The patient rapidly became delirious, semistuporous, and the pulse weak. In rapid succession, his doctor gave 2 ampules of epinephrine, atropine sulfate gr. 1/150, and an ampule of epinephrine in oil, but without any apparent effect. He was brought to the hospital by the police rescue squad, who gave him oxygen en route. When first seen, he was semistuporous, his face flushed and cyanotic, the heart sounds not audible, the lungs filled with coarse rhonchi, temperature 103.2° F., respiration 24, the pulse regular at 140 per minute, and the blood pressure uncertain at 60/0. In the

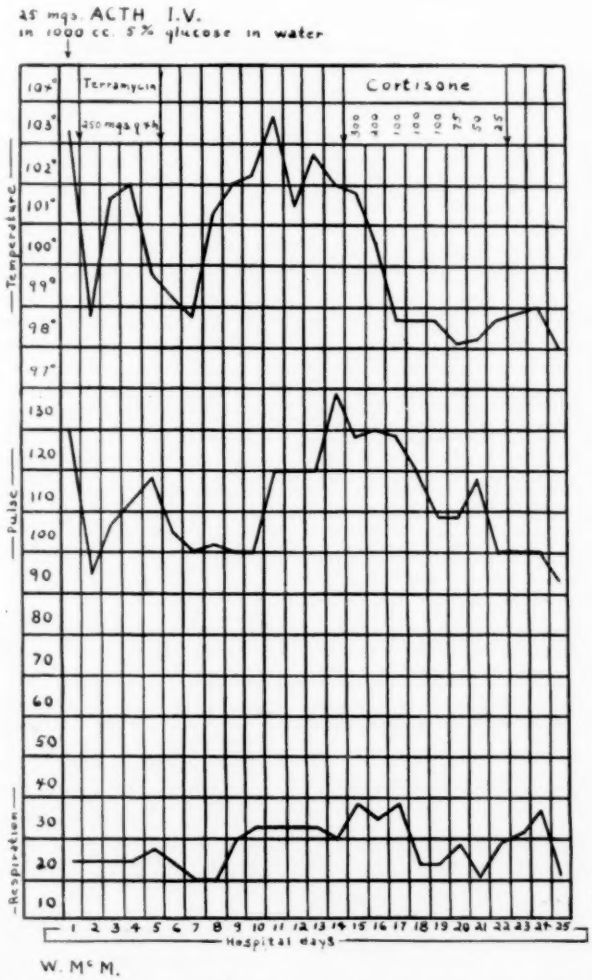

Fig. 1.—Response of temperature, pulse, and respirations of Case 1 to indicated therapy.

receiving ward, he was given oxygen by mask, an intravenous drip of 5% glucose in distilled water was started, and then 25 mg. of ACTH was injected slowly into the tubing of the drip. Color, pulse and respiration gradually improved, and he was transferred to a hospital room where the intravenous drip was continued, and norepinephrine added to the drip. The blood pressure slowly rose, and by 9.00 p.m. it had reached 78/50, and 5 hours later was 92/54. He had, in the meantime, become mentally clear and alert.

The course of events may be related to the accompanying clinical chart (Fig. 1) on which is recorded the highest temperature of each day. During the first 8 hours, the temperature fell to normal and so remained during the next day. Then fever returned, and there was much purulent sputum, suggesting active infection. He was given terramycin for 4 days with temporary lessening of fever, only to recur 2 days later. Yet, the patient appeared amazingly well and no clinical or roentgenological evidence of pneumonitis could be found to explain his fever. The leukocyte count was only 10,000, and the differential smear showed no eosinophils.

Because of the absence of any objective evidence of infection other than fever, because of several negative blood cultures, and because there was present itching urticarial lesions, it was felt that both fever and urticaria was the continued evidence of an allergic reaction. It was, therefore, decided to treat him with cortisone. He received 300 mg. on February 14, 200 mg. on February 15, 100 mg. daily for the next 3 days, and then successively 75, 50, and 25 mg. Fever and urticaria promptly cleared up and the patient's further recovery was uneventful. He was discharged from the hospital on February 24, 1953. Prior to discharge, he was found to give a positive immediate cutaneous reaction to penicillin, and passive transfer studies demonstrated the presence of circulating antibodies.

Comment. In this case of anaphylactic shock, prompt availability and use of epinephrine by his physician probably saved this man's life. Intravenous ACTH drip secured the situation. The protracted nature of the reaction, lasting over 2 weeks, and attended by fever should be stressed. This posed the problem of differential diagnosis between infection and reaction. The diagnosis of reaction alone was confirmed by the effect of cortisone therapy, unaided by any antibacterial treatment.

CASE 2. S. P., a 65-year-old white male, was admitted to the hospital on January 25, 1953, for an acute myocardial infarction. In addition to the usual treatment, he was given on admission a prophylactic injection of 300,000 units of aqueous procaine penicillin. On the twelfth hospital day, he developed a macular erythematous eruption over the trunk and extremities and, at the same time, a low grade fever, which had been present since admission, increased, with daily spiking rises up to 101° F. Those in attendance, fearing a pneumonitis, ordered aqueous procaine penicillin every 12 hours. The temperature then returned to normal for a week, confirming the belief that the fever was due to infection. The rash, however, became progressively worse. By the twentieth day, there was a generalized exfoliating dermatitis, and the fever recurred with daily rises to 102° F. The blood at this time showed an eosinophilia of 12%.

At this point, we suggested that both fever and rash were due to penicillin, and that further penicillin medication should be stopped, and a course of cortisone begun. For several days, Pyribenzamine was used in full dosage, but with little effect on the rash and none on the fever. On the twenty-fifth hospital day, cortisone was begun, 300 mg. the first day, 200 mg. the second, and then 100 mg. daily for 5 days, and then discontinued. The temperature became, and remained, normal after 24 hours. The skin condition rapidly improved, and he was discharged asymptomatic on the forty-third hospital day.

Comment. An injection of a depot penicillin produced sensitivity, as well as furnished the shocking dose that brought on a rash. The added use of penicillin aggravated the condition to the point of an exfoliative dermatitis. Again, fever at first suggested infection, and led to additional unwise penicillin therapy. Cortisone treatment promptly proved both rash and fever to be on an allergic basis.

CASE 3. C. G., a white male, age 43, had received penicillin for the first time in 1945, as an out-patient, because of a "cold" without fever. About January 1, 1953, in an attack of influenza, he was given an injec-

tion of penicillin. In 2 days, he began to have hives that persisted in spite of various attempts at medication, including Pyribenzamine, 100 mg. of cortisone daily for 2 weeks, and finally ACTH by intravenous drip for 4 days. He was having recurrent crops of hives daily when first seen on March 13, 1953. In addition, for 2½ weeks, he had fever, and for about the same time pain and swelling in various joints. He gave a history of sensitivity to strawberries, first noted in 1952, and of recurrent headaches attributed to sinus disease. His father had been asthmatic for many years.

In spite of the failure of previous treatment, it was felt that he had a "serum sickness" type of penicillin reaction. In addition, there was feared the possibility of early periarteritis nodosa. He was accordingly put on cortisone 300 mg. the first day, 200 mg. the second day, 100 mg. daily for 5 more days, and then 75, 50, and 25 mg. on the last 3 days, respectively. In addition, he was told to restrict his diet to cooked foods only, and to avoid fish, sea food, nuts and chocolate. The hives promptly stopped and for 3 weeks he had no other symptoms. Then, there occurred occasional sharp swellings of a lip, or a hand, or a foot, at intervals of about 2 weeks at first, but then more frequently, and lasting from 2 to 4 hours. There was no fever and no joint manifestations.

Early in July, he was subjected to a series of skin tests, and was found sensitive to a number of foods, the avoidance of which was followed by clinical relief.

Comment. In this patient, a "serum sickness" type of reaction to penicillin managed to increase and bring to the surface a food allergy which had to be recognized, and its causes avoided, before lasting relief was obtained.

Summary and Conclusions. 1. Penicillin is the commonest cause of drug allergy.

2. Manifestations of penicillin sensitivity cover almost the whole gamut of allergic reactions and immunological mechanisms.

3. The severest is that incident to anaphylactic sensitivity, and its greatest danger lies in death from anaphylactic shock.

4. Exfoliative dermatitis and severe irreversible vascular reactions, possibly going on to periarteritis nodosa, contribute additional allergic deaths.

5. Individuals with a personal or familial history of allergy are more easily sensitized to penicillin, and furnish the majority of severe and fatal penicillin sensitivities.

6. Much penicillin sensitivity is unnecessary, and preventable by not giving penicillin in minor ailments, avoiding local applications of the drug, avoiding preparations of depot penicillin unless they are decidedly necessary, giving preference to the oral route of administration, and avoiding combined parenteral injections with other possible antigens.

7. The most dangerous type of penicillin sensitivity, anaphylaxis, can be usually recognized by skin test, especially by the immediate whealing reaction on cutaneous or intracutaneous testing, and at times in lesser degrees of sensitivity, also by the delayed (24 to 48 hour) intracutaneous reaction.

8. Penicillin reactions may be largely avoided by careful attention to an allergic history in the patient's background, by questioning with regard to previous penicillin therapy, especially previous penicillin reactions, and by proper precautions in the management of such patients.

9. The oral route of penicillin administration should be preferred to parenteral routes.

10. If parenteral administration is necessary, the injection should be into the arm only, and at a low enough level so that it will not prevent the effective use of a tourniquet in case of severe reaction.

11. The treatment of the several types of penicillin reactions is presented. Emphasis lies in preparedness to meet the emergency of anaphylactic shock.

ADDENDUM: *Case 18.* An additional fatal case of anaphylactic shock was encountered by one of us (R. A. K.) in an overseas Army installation. A young male, in July, 1953, at a dispensary was given an intragluteal injection of penicillin for neisserian urethritis. Within a few minutes a shock picture developed for which active treatment was undertaken. He appeared to react very favorably and he was then put into an ambulance to be moved to a nearby Army hospital. On the way, shock symptoms rapidly returned and the patient died within two hours of the penicillin injection. At necropsy, Major J. T. Elston (who will report the case in detail) found adrenals with distinctly less cortical tissue than normal. No information was available as to previous penicillin therapy or any allergic history. The case illustrates (a) the need for *prolonged* shock treatment, as with cortison or ACTH, since the depot penicillin remains to produce shock if therapy ends too soon, and (b) the desirability of an injection site (arm) from which the absorption of the penicillin can be stopped by tourniquet.

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CORRELATIONS IN CLINICAL AND EPIDEMIOLOGICAL INVESTIGATION*

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It is something more than an honor to be asked to give the third in a series of lectures honoring Doctor Wadsworth, who has but recently reached his majority for the fourth time. It is a rigorous pleasure, largely because since my first acquaintance with him and his endeavors, he has represented the standard of excellence. Doctor Wadsworth became to us in clinical medicine and investigation the impersonation of dependable biologics. It is important that from the start, as now, it was the Division of Laboratories and Research which he guided. And in the Preface to the original edition of "Standard Methods" he pointed out its practical aim in direction of inexperienced workers but that standardization must not interfere with the other objective, stimulation of research. This point of view has persisted.

In their article on the public health laboratory, Doctors Wadsworth and Dalldorf emphasize that it is a unique part of public health, and an American institution. So is Doctor Wadsworth. And because of his continued interest in the relation of the laboratory to clinical investigation, I have chosen the title of my lecture, but with clear realization that it misses by far the standard required on this occasion.

It has become commonplace when comparing epidemiology and clinical medicine, to say that the latter concerns itself with the individual patient while in epidemiology it is the sick community. It is a summary statement which assumes that understanding of it is as general as its use. Moreover, there is a great tendency to create a cleavage between the two fields which should be eliminated if our objectives in preventive medicine toward broader appreciation of the community aspects of disease are to be furthered. For example, a recent article[9] on epidemiology states: "Clinical medicine is concerned with the reaction between the human host and the microparasite when it results in manifestations sufficiently marked to be regarded as an 'illness.' Moreover, it is centered upon one phase of the relationship, that is, from the time of onset of symptoms to recovery or death. On the other hand, epidemiology is concerned with the whole relationship from the time the microparasites enter the body until they are eliminated. Interest is extended to include the conditions under which transmission of infection takes place, the period of time which thereafter elapses before the appearance of symptoms, the occurrence of reactions below the threshold of clinical recognition and the duration of the infectious state." This statement is quite disturbing because of its arbitrary restriction of clinical horizons and by its lack of invitation to expansion of interest.

Greenwood, in 1935[6], referred to "the meagre *epidemiological* philosophy which has grown out of laboratory studies" and says " . . . that although they have provided some of the material for the synthesis which must be made before we can formulate epidemiological 'laws,' they have no more sufficed than did the data of pre-experimental descriptive or even of 'classical' epidemiology to describe

* The third Augustus B. Wadsworth Lecture delivered November 14, 1952, at the meeting of The New York State Association of Public Health Laboratories.

either the secular variations of disease-prevalence or even the immediate course of an epidemic." It can be pointed out that since the time of that statement there have been great advances in knowledge of the intimate characteristics of many infectious agents, of the mechanisms involved in disease processes, of different etiologic entities which may have been grouped under a generic heading, in the scope of detailed studies in populations, and in the appreciation of the standards to be met to give significance to biological data. There has been above all a broadened front on which the laboratory and the clinic or the field have been brought together for interpretation of a problem. Moreover, Professor Greenwood was fully appreciative of the situation, for in a paper published in 1946[7], he concluded that mathematical statistics alone, without an understanding of the biological conditions, will not do much towards solving the problem of epidemics. His understanding of the need was further evidenced by his concentrated interest in experimental epidemiology.

It is my purpose to present correlations between the approaches of clinical and epidemiologic investigation and to emphasize the participation of the laboratory in these activities. For, as the laboratory participates in examination and study of the patient and the patient makes up the group which furnishes the epidemiological event, the interrelationship is apparent. It is this theme to which I would speak. Perhaps the term "clinical epidemiology" which we have defined previously helps. "It would consider the individual case within the epidemic and by application of the methods of clinical investigation to the study of disease in its natural habitat would build. . . . .information which could subsequently serve as the basis for accurate epidemiological conclusions"[4]. To my mind epidemiology has a major concern with the natural history of disease; hence, those features observed in the patient must be a significant part of the understanding of reservoir, transmission, causation, pathogenesis, ultimate course, and immunity.

Epidemiology is not a simple precise methodology but one which employs, as does clinical medicine, a variety of interests and disciplines for understanding of a problem. The extent to which the two become unrelated is to some degree a measure of our failure in medical education to awaken a dormant interest in the broader relationships; the degree to which the fundamental principles and interests which draw men to clinical medicine can be attracted toward the group concepts of epidemiology may reflect the amount of encouragement given to consider the chains of events involved in the phenomena of disease or other abnormality. And it seems clear that it is the point of view which, in the end, is the determining factor, not the definition, because epidemiological problems can be approached from many angles and with many skills. The physician with a mathematical bent may readily enter the field of statistical epidemiology, but so may others. Is the early detection of cancer clinical or is it important epidemiologically, also? Is the laboratory investigator working with causative agencies related to individual patients not furnishing data of epidemiologic significance? The physician who looks beyond the bedside for understanding of the phenomena the patient presents is broaching the epidemiologic concept and in many instances the epidemiologist must depend on correlations beginning at the bedside for his take-off. Greenwood has pointed out that "Epidemiology, the mass aspects of disease, where not the sick individual but the group, the herd, is the unit of

observation, is a very old subject of inquiry; it has interested most of the great physicians from the dawn of knowledge to now."[8] It was clinical epidemiology. The effort to find an orderly interpretation of a disease phenomenon has been a basic concept of medical thought; the avenues through which contributions are made vary considerably.

A parallel can be seen in the plans of clinical and epidemiological investigation. But as the data obtained from a single patient may not give total understanding of the disease process, neither do the data from one epidemic ordinarily provide complete understanding of the mass problem. It is to meet these deficiencies that further investigation and special studies are so greatly needed.

It is interesting, then, to pursue the analogy of the study of the patient and of the community somewhat farther to point out how the investigative procedure employed in the study of the one follows the same orderly basis applicable to the other and how readily the extension of concept can be made. While the outline may proceed primarily on the basis of infectious disease, it should be pointed out at this stage that its transfer to non-infectious problems is readily apparent (Table 1).

TABLE 1.—ANALOGIES IN THE STUDY OF DISEASE IN THE PATIENT AND IN THE COMMUNITY

	Patient	*Community*
	1. HISTORY	
A. *Complaint*	Major symptoms	Cases of disease
B. *Present Illness*	Onset: first symptoms	Time of first case or cases
	Development: abrupt gradual	Abrupt or gradual
	Course to present	Number of cases to present
	Localization of symptoms	Localization of cases Time Geographic Occupation Age Sex
C. *Past History*	Previous attacks	Usual incidence based on prior records.
	Is this acute or chronic?	Is this epidemic or endemic or unusual?
	Any preceding exposure or predisposing disturbance	Unusual incidents such as migration, break in sanitary controls, invasions of animals or insects, weather
	Other illnesses	Past occurrence of other similar diseases
	Immunization or other prophylactic measures	Immunization programs and sanitary status
	General health	Vital statistics
D. *Family History*	Family roster	Character of communities in the general area
	Similar illnesses in family (genetic or contact)	Cases in other nearby communities
	Other illness in family	Other illness in area
	Usual habits, activities, and stresses	Usual sources of water, milk, food, sewerage Type of population and industry Usual social activities
	Economics	Economic conditions
	Visitors or visits	New arrivals or exposures
	Illness in domestic animals or pets	Epizootics in animals

TABLE 1.—*(Continued)*

	Patient	*Community*
	2. Physical Examination	
A. *Clinical*	Vital signs	Establish diagnosis when possible
	Inspection	Detailed description when not recognized
	Palpation	Case finding
	Percussion	Proven reporting and mapping
	Auscultation	Accurate histories
		Atypical cases
		Association between cases
		Distribution and congregation of cases
		Secondary and multiple cases
B. *Environmental*		Geography and topography
		Density of population
		Examination of water, milk, sewage disposal, food supplies and their routes of distribution
		Economic and housing conditions
		Location and nature of industries
		Pollution
		Insect, rodent, animal population
		Special communal facilities: swimming pools, etc.
C. *Laboratory*	Clinical laboratory tests	Confirm diagnosis or establish it
	Special studies	To demonstrate causative agent, if possible
		To demonstrate degree or extent of immunity
		To indicate strategic approach to control
		To determine the potential
D. *Statistical*	Summary of findings	Analysis of data regarding incubation period, symptoms, morbidity, mortality, case fatality
		Secondary cases—communicability
		Pathogenicity—typical vs. atypical
		Selective distribution—age, sex, occupation, family
		Establish correlations
		Effect of control measures
		Comparison with control data for validity
	3. Diagnosis	
	Nature of case	Nature of epidemic
		New introduction or epidemic recurrence
		Source
	4. Treatment	
	Clinical handling by family physician and hospital staff	To notify state and federal agencies
		To arrange hospitalization and care
		To mobilize community public health and medical resources
		To institute control programs against:
		Reservoir
		Distributor
		Susceptible
		To allay public
	5. Course	
	Description of course and effect of therapy	Epidemic course and the effect of control measures
	6. Outcome	
	Recovered	Stopped by control measures
	Improved	Reduced by natural or control measures
	Chronic stage	Endemic with recurrences
	No improvement	Prolonged epidemic period
	Death	Decimation of highly susceptible population

To further this amalgamation it is well to turn to examples of different ways in which the clinic and the laboratory have in recent years provided the basis for the advancement of epidemiologic understanding of a number of disease problems.

A splendid starting point is here in Albany with the example of the recognition of a virus in search of a disease. The demonstration of Coxsackie virus from cases of illness during the poliomyelitis season seemed to lead to an easy conclusion[3]. Rapidly, evidence accumulated of widespread distribution and Doctor Dalldorf showed the differences in pathological features produced by different strains of the virus in mice to be sufficiently distinct as to represent group characteristics. The subsequent clinical contribution has been to distinguish two widely different diseases, herpangina and epidemic pleurodynia, associated with the Group A and Group B Coxsackie viruses, respectively. This oversimplified recitation well illustrates how investigation of illness in which the laboratory played its proper conjoint role with clinical observation provided a firm basis for analysis of an epidemiological problem of wide interest and importance. Then you may ask "Wasn't that all epidemiological in character?"; to which I would reply "Yes, but it was also pathological, clinical, investigative."

A somewhat similar situation has existed in relation to what we have called influenza C. Taylor[10] isolated a virus in 1947 and obtained limited serological indication that it was related to respiratory disease in man. On the other hand, he concluded that it was probably of no public health importance. In studying a strain of the same nature isolated in our laboratory, attention was attracted by the great frequency of high titers of antibody in the blood of the adult population and by the fact that this was so as far back as 1936[5]. Since that time, additional strains have been isolated and clinical records have indicated that the disease resembles mild influenza, but in other instances the infection may be largely subclinical. It is of considerable importance to know the clinical picture adequately, but at present we are only aware of a widespread infection and a well defined virus but are still in search of the disease characteristics. It is an instance in which the clinical information is needed to amplify laboratory data so as to permit mapping of the epidemiological pattern.

The converse pattern of information, that is, the disease without an agent, has been a more common experience. It is, nevertheless, of value to examine certain situations briefly for the correlations involved. This is particularly true of the field of acute respiratory disease. Although influenza has been repeatedly referred to as the "crux of epidemiology" and its clinical and general epidemiological features were clearly established, it was the extension of knowledge through participation of the laboratory in detailed clinical epidemiology which has given body to the understanding of recurrence. In fact, I don't believe any disease in history has been studied with as many individual patients subjected to the combined clinical etiological laboratory examination as has influenza. And much of the intensive effort to fix cycles of 51 weeks, 3 years, or 30 years seems metaphysical in the light of current information concerning variation in types, strains, and in other characteristics. The thesis of an orderly purposeful mutation presumably forced by the immunity process of the population, which is advanced by present-day cyclists, seems equally unsound, since it maintains that old viruses fade away and are completely replaced by new. But in the case of influenza clinical and epidemiologic interpretations remained uncer-

tain until knowledge of etiology, the devising of diagnostic procedures and the study of more patients, gave clarification. It was in this connection that our use of the term *clinical epidemiology* was begun, and it was the search for virus in relation to lobar pneumonia, suggested by clinical observation, which provided our personal introduction to the virus field.

The information which led to an appreciation of primary atypical pneumonia was essentially clinical in character. It was at a time when great effort was being made to obtain typing of pneumococci in patients with pneumonia so as to permit early treatment. It was also a time when Roentgen-ray became more widely available in group populations and when the successful treatment of bacterial pneumonia with sulfonamides was being realized. The magnificent studies of the Commission on Acute Respiratory Disease provided the epidemiologic pattern in military populations, demonstrating that pneumonia was incidental to the infection, another accident of infection. They further acquired evidence in human volunteers that perhaps two, rather than one, agents were involved[2]. The incomplete state of this problem can be attributed to a deficiency on the laboratory side to keep pace with the other developments.

To a large extent the separation and identification of Q-fever came from efforts to determine the etiology of a form of atypical pneumonia observed clinically. The epidemiological circumstances repeatedly suggested that the pneumonia was of special etiology, but only when laboratory diagnostic procedures were devised did the distribution of, and mechanisms of, infection take form. In this case, however, progress along all three lines has developed more evenly.

Somewhat different circumstances surround the development of knowledge concerning histoplasmosis. The epidemiological studies of tuberculosis in Tennessee and surrounding areas had shown that in certain regions pulmonary calcification occurred early, and was not associated with positive tuberculin tests or increased mortality. In other regions the usual pattern of tuberculous correlations was observed to predominate. Although the data strongly urged the conclusion that two different diseases were being encountered, it was insisted on the contrary that tuberculin tests were at fault. But the first data of significance relating the high frequency of calcification with negative tuberculin tests to histoplasmosis were from studies on clinical wards[1].

Many examples from other fields can be cited. It may only be necessary to mention the growing field of leptospiral infection to indicate the manner in which identification of different species of this agent, associated with varying clinical pictures and heterogeneous infection chains is rapidly modifying the entire concepts of leptospirosis. The recognition in the United States of *L. pomona*, with disease of swine and man; of *L. bataviae* with disease of horses and probably man; of *L. autumnalis* and its identification with Fort Bragg fever; the relation of leptospirosis to aseptic meningitis, are all examples of correlation of laboratory and clinical study to the advancement of epidemiology.

In pursuing this line of argument, it is not intended to imply that recognition of etiologic agent, the clinical manifestations and the chain of transmission, constitutes all of epidemiology. But without these data the development of the mass laws is more likely to be beset with difficulties. Many examples of this fact could be recounted. Nor is it intended to discount the fact that epidemiologic characteristics are in many instances so typical that variations from them may point to different

biological sequences or different etiologic agents. This was true of Maxcy's studies of endemic typhus and in the disclosure of jungle yellow fever. Furthermore, it is thoroughly agreed that explanation of disease in the herd requires understanding of the laws of mass action which govern the interactions of the different components in the involved herd, just as they are required for understanding of the behavior of complex organic reactions in various media.

The purpose has been to invite the clinician and the diagnostic laboratory worker to extend their horizons rather than to restrict them. By considering the patient as a member of an affected community or as one illustration of an extensive problem, the physician of the community may be stimulated from his records of experience to study the laws and factors which govern the occurrence and course of disease or abnormality in a population. And as more information of the origins of various diseases is acquired, as diagnostic procedures can be more readily applied, the greater the opportunity and rewards in clinical epidemiology. I would repeat that pathogenesis is an integral part of the natural history of disease; that knowledge of causation is a powerful force for understanding of the participating factors and their interrelationships. They are indeed the material for the synthesis of epidemiological laws.

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OBSERVATIONS ON THE NATURAL HISTORY OF GASTRIC CANCER

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Recent experience with carcinoma of the stomach has emphasized the rather long duration of symptoms in some patients before the correct diagnosis is made. The duration of symptomatology with its relation to medical care, location of the lesion and pathology was analyzed in proven cases of gastric cancer, in order to ascertain the reasons for delay in diagnosis.

Material. Sixty patients from the medical and surgical services of the Maimonides Hospital of Brooklyn formed the basis of this study. They represent all the cases of proven gastric cancer since 1948.

The analysis of these patients' histories include the duration of symptoms; history of bleeding; change in symptomatology; presence of other gastrointestinal disease; and history of gastrointestinal investigation. No mention of the symptomatology of gastric cancer or of individual complaints will be made as these have been well documented[7].

Results. DURATION OF SYMPTOMS. Of 60 cases, 32 (50.3%) had symptoms of less than 12 months and 11 (18%) of less than 2 months' duration. On the other hand, 28 (49.7%) had symptoms of over 12 months' duration and six of these, (10%) had symptoms of 48 months or longer. (Fig. 1). It is this group of 28 patients, designated Group B, which comprises the basis of this report. Such a large group of patients in this category might suggest that gastric cancer can be a rather slow growing tumor or that some predisposing symptomatic lesion in the stomach was present. In either case, earlier diagnosis during this period should increase the survival rate of patients with gastric cancer. An analysis of the factors which delayed diagnosis in Group B follows.

MEDICAL CARE AND GASTROINTESTINAL INVESTIGATIONS. Twenty-five of the 28 patients had sought medical advice at least once during the course of their disease, and in most cases were under continuing treatment. In addition, 18 patients had had a gastrointestinal Roentgen-ray series at least once, several more than once, and one female patient had had a gastrointestinal Roentgen-ray series annually for 5 years prior to admission. Six of these 18 patients had roentgenologic evidence of gastric ulceration, but they were treated as benign ulcers for periods ranging from 1 to 3½ years. In the remaining 12 patients there was a diagnosis of peptic ulcer in 4 patients which was later confirmed by surgery in 3. Immediately prior to hospitalization repeat gastrointestinal roentgenograms were suggestive of gastric cancer in many of the patients. In others, no roentgenograms were taken and the presence of a mass, an anemia, or metastatic disease led to the suspicion of cancer.

LOCATION OF THE LESION IN GROUP B. All locations were represented without a preponderance of any one. Of the 6 patients whose symptoms were of 48 months' duration or longer, there were 2 prepyloric lesions of which one was annular; 2 pars media lesions involving the lesser curvature; one lesion involving the whole lesser curvature and

one the cardiac end of the stomach invading the esophagus. No type of histology predominated. In this group of 6 patients, there was one signet cell, 3 adeno-, and 2 anaplastic carcinomata. In the remaining 22 cases, there was also a rather equal representation of all locational and histological types.

PRESENCE OF OTHER GASTROINTESTINAL DISEASES. Since location and histology could not be correlated with the duration of symptoms, or with the accuracy of diagnosis, it was thought that gastric cancer might perhaps be obscured by other gastrointestinal diseases. Such may have been the case in 7 patients. Four of these had roentgenologic evidence of duodenal peptic ulcer, 2 had gallstones and one had roentgenologic evidence of spastic colon. All 7 had been treated for these diseases, and had had, sometime during the course of their disease, a gastrointestinal series interpreted as negative for cancer of the stomach. The presence of peptic ulcer, proven by surgical exploration, in 3 cases is interesting since it refutes the previous inference that gastric cancer and duodenal peptic ulcer are mutually exclusive[2].

EVIDENCE OF HEMORRHAGE. Three patients of 28 had large gastric hemorrhages at significant intervals before surgery; 3½, 2 and one year prior to admission. Two of these patients were treated for gastric ulcer because of roentgenologic evidence of gastric ulceration and at the time of histological examination one of these showed a possible transition from benign to malignant ulcer, while the other one showed a classical appearance of adenocarcinoma in which there was no histological evidence of transition. The third patient is one of the group who had both a peptic ulcer and a carcinoma of the stomach at the time of surgery. We cannot determine whether this patient bled from his peptic ulcer or the carcinoma. Many of the remaining 25 patients had episodes of bleed-

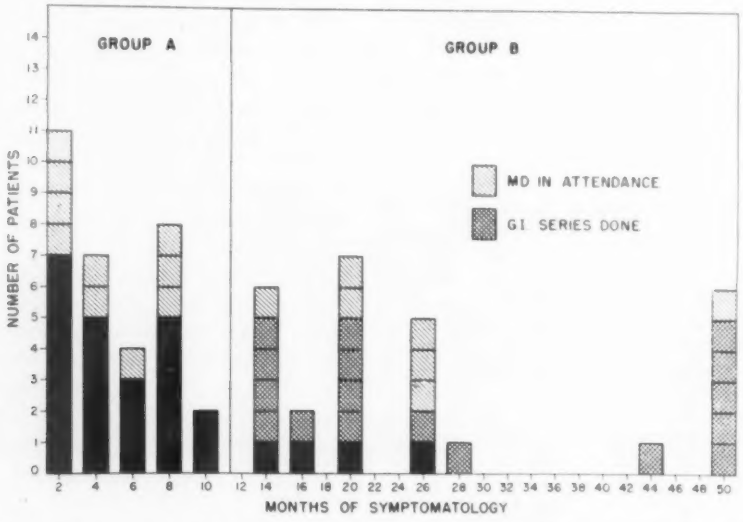
GROUP A
GROUP B
MD IN ATTENDANCE
GI SERIES DONE
NUMBER OF PATIENTS
MONTHS OF SYMPTOMATOLOGY
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50

Fig. 1.—Most of the cases in Group B occur in the 12 to 28-month range, but 6 cases had symptoms for as long as 48 to 50 months. The vast majority of patients had a gastrointestinal series and physician attendance during the course of their disease.

ing which did not occur at significant intervals before surgery, but rather were the reason for hospitalization.

Discussion. Any analysis of the symptomatology of gastric cancer must take into account the often argued question of whether a benign gastric ulcer becomes malignant or not. In this study we found one pathological specimen wherein that may well have occurred. Comfort and his group believe that this may occur in 10% of all benign gastric ulcers[4]. Certainly one must entertain the possibility that this transformation occurs more frequently than generally thought. We acknowledge the possibility that this may have occurred more frequently in our study, but either undeniable or suggestive histological evidence for this was lacking. Possibly one might assume that the patients in Group B, did not have gastric cancer during the entire period of symptomatology, but some predisposing lesion instead, such as gastritis, benign tumor or gastric ulcer.

It may also be argued that, in those instances in which symptoms existed for years, the assumption that we were dealing with a slowly growing tumor is just as tenable. The observation has been made by others that gastric cancer may be a slowly growing tumor when symptoms are most prominent[7,9,11]. Should the 6 patients who had roentgenologic evidence of gastric ulcer be removed from the study because of the possibility that they were transformed malignancies, there would still be left a significant number of patients who had symptoms for years. From our study we cannot contribute further clarification of this issue. Whether we are dealing with transformation, slowly growing tumors, or a substrate for the development of cancer, the patient with gastric ulcer or persistent gastric symptoms will best be served by earlier surgical intervention.

In many instances roentgenological studies had been made and had failed to reveal a diagnosis of gastric cancer, yet at surgical-pathological examination, all the lesions were in accessible locations for accurate roentgenologic diagnosis. This is not surprising since the terminal anatomical position of the tumor cannot be correlated with films taken much earlier in the course of the disease. It is agreed that roentgenologic examination of the stomach will reveal the lesion in 85 to 95% of patients with gastric cancer[9]. These figures, however, do not include patients who had prior negative examinations. To our knowledge no study has ever been made which has reported on repeated negative gastrointestinal Roentgen-ray examinations in the patient with symptoms. Others have reported on the inadequacy of the gastrointestinal roentgenologic series in any one examination[6]. However, neglect of this consideration has led to a complacency on the part of the physician when the gastrointestinal series has been reported as negative for cancer.

There appear to be 3 classes of patients within Group B; those thought to have gastric ulcer, those with significant hemorrhage either due to unknown cause, or associated with Roentgen-ray evidence of peptic ulcer and those in whom no explanation of symptoms was available. We believe that treatment aimed at the survival of these classes must be bold and imaginative. The following considerations are presented for the proper management of these patients.

1. Gastric ulcer is a surgical disease, and not a disease that may be medically treated for an arbitrary period of 6 weeks or longer before surgery[8]. It is well recognized that 10 to 15% of gastric ulcers, seemingly benign, are actually malignant[3].

2. Unexplained gastric hemorrhage is a surgical disease. Three of our patients

had severe hemorrhages one to 3 years before surgery. By the term "unexplained" we mean that complete investigation of the patients has not revealed a cause of the bleeding.

3. For the diagnosis of gastric cancer, the roentgenologic examination is but one tool, and should be complemented by gastric analysis[5], endoscopic examination[1], gastric washings and Papanicolau staining[10].

4. In the absence of demonstrated pathology, continued unexplained gastrointestinal distress should be treated by laparotomy. This can be of more value and is more conservative therapy than repeat roentgenological and endoscopic examinations.

Conclusions. 1. The histories of 60 patients were analyzed for duration of symptoms in relation to location and histology of cancer of the stomach.

2. Approximately 50% of these patients had symptoms of over 12 months' duration.

3. The vast majority had roentgenologic investigation and almost all had had a doctor in attendance during the course of the disease, yet the diagnosis was not made during the most favorable period for gastric resection.

4. Suggestions for the treatment of gastric ulcer, gastric hemorrhage, and undiagnosed gastric disease are presented. These may well affect the survival rate of patients with gastric cancer.

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THE PULMONARY MANIFESTATIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS

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The collagen diseases are disorders of the connective tissue of the body, usually involving multiple organs. Pulmonary involvement has been described in each of the principal collagen diseases: rheumatic fever, periarteritis nodosa, disseminated lupus erythematosus, scleroderma, and dermatomyositis. For the most part, however, the pulmonary lesions represent either rare manifestations of common diseases, as in rheumatic fever, or incidental features of rare diseases, such as periarteritis nodosa. The pulmonary manifestations of lupus erythematosus have received little attention; the frequency of pulmonary involvement has not been emphasized in most descriptions of this disease. The recent development of a useful diagnostic test has stimulated interest in disseminated lupus and has demonstrated it to be more prevalent and more protean than previously thought. It seemed desirable, therefore, to investigate more fully the nature and frequency of pulmonary changes in this disease.

A review of records at the Philadelphia General and Graduate Hospitals disclosed a total of 22 patients with well established diagnoses, between 1947 to 1951, 7 at the Graduate Hospital and 15 at the Philadelphia General Hospital. The diagnosis was confirmed by necropsy in 9 instances, supported by demonstration of L. E. cells in an additional 7 patients, and was considered authenticated in the remaining 6 instances by characteristic skin lesions and typical clinical and laboratory findings.

Roentgenological or pathological evidence of pulmonary or pleural disease was found in 20 of the 22 patients (Table 1). Pulmonary or pleural disease was noted on 25 of the 33 hospital admissions of these patients (Table 2). Fifteen of the patients showed on one or more admissions clinical and roentgenological evidence of pneumonia (Figs. 1, 2). In 2 other patients, previously unsuspected pneumonia was found at necropsy. Roentgen-ray study disclosed the diffuse perivascular or vascular changes which have been considered characteristic of the collagen disease in only one patient. Two patients had pleurisy with large effusions.

In some instances, there were frank symptoms and signs of pneumonia, and Roentgen-ray examination disclosed lobar consolidations. More often, the respiratory symptoms were overshadowed by the systemic toxemia, and physical signs were minor; in such cases the roentgenological appearance was usually that of patchy pneumonia. These processes were, as a rule, acute, but occasionally resolution appeared to be tardier than normal.

Sputum cultures yielded, in most instances, mixed growths of the common respiratory tract organisms, including pneumococci and streptococci. Cold agglutinins were sought in 4 cases; in none were they demonstrable. Of special interest were the effect of pneumonia upon the leukopenia of lupus erythematosus. Three patients developed frank leukocytosis, with counts of 17,700, 15,000 and 14,500. Seven other patients had leukocyte counts ranging

TABLE 1.—CHEST FINDINGS IN 22 PATIENTS WITH DISSEMINATED LUPUS ERYTHEMATOSUS

GRADUATE AND PHILADELPHIA GENERAL HOSPITALS

1947 TO 1951

Pneumonia	
Detected by roentgenogram	15
Detected by necropsy	2
Pleural Effusion	2
Diffuse Pulmonary Infiltration	1
Negative Chest Films	2

TABLE 2.—ROENTGENOLOGICAL AND PATHTOLOGICAL FINDINGS IN THE CHESTS OF 22 PATIENTS WITH DISSEMINATED LUPUS ERYTHEMATOSUS

Philadelphia General and Graduate Hospitals 1947 to 1951

Patient	*Age*	*Sex*	*Race*	*Admission*	*Chest Roentgenogram*	*Necropsy*
H.K.	25	F	W	11–11–46	Pneumonitis	*
E.S.	35	F	W	12– 9–46	Pneumonitis	*
L.M.	33	F	N	3– 9–47	Diffuse pulmonary infiltration	*
F.T.	30	F	W	7–28–47	Pneumonitis	*
C.O.	27	F	N	3– 9–45	Negative	*
				6– 2–47	Negative	*
				7– 7–47	Negative	*
				11–12–47	Negative	Bronchopneumonia
H.V.	44	F	N	9–10–47	Bronchopneumonia	Bronchopneumonia
M.O.	35	F	W	3–31–48	Negative	*
				6– 2–48	Pneumonitis	**
J.N.	25	M	W	10– 9–48	Pneumonia	Organizing pneumonia
W.H.	12	M	N	1– 1–49	Negative	Bronchopneumonia
J.B.	30	M	N	8–16–49	Minimal tuberculosis	*
				11–30–49	Pneumonitis	Pneumonia
R.B.	22	F	W	8–25–49	Pneumonitis	Bronchopneumonia
E.J.	25	F	N	9–20–49	Pneumonitis	*
				10–18–50	Pneumonitis	**
S.S.	44	F	W	1– 1–50	Negative	*
				8–19–50	Pneumonia	*
				11– 7–50	Pulmonary edema	Pulmonary edema
L.S.	41	F	N	5–26–50	Pneumonia, RLL, RUL	*
				9– 5–50	Pneumonia, RUL	*
A.B.	16	F	W	12–15–50	Pneumonia	*
				5–24–51	Negative	*
E.B.	30	F	W	2– 9–51	Negative	*
E.T.	35	F	N	3–24–51	Bronchopneumonia	*
A.H.	24	F	W	5–24–51	Pleurisy with effusion	**
E.P.	57	M	N	8–21–51	Pleurisy with effusion	*
E.M.	33	F	N	8–24–51	Pneumonia, pleuritis	Pneumonia, pleuritis
J.D.	31	F	W	12–18–51	Negative	*
V.B.	31	F	N	12–20–51	Lobar pneumonia	*
				10– 5–52	Bronchopneumonia	Pneumonia

* Discharged alive
** Died. No necropsy

Fig. 1. Case V. B. – Roentgenogram showing right upper lobe pneumonia. Complete resolution was demonstrable on examination 2 weeks later.

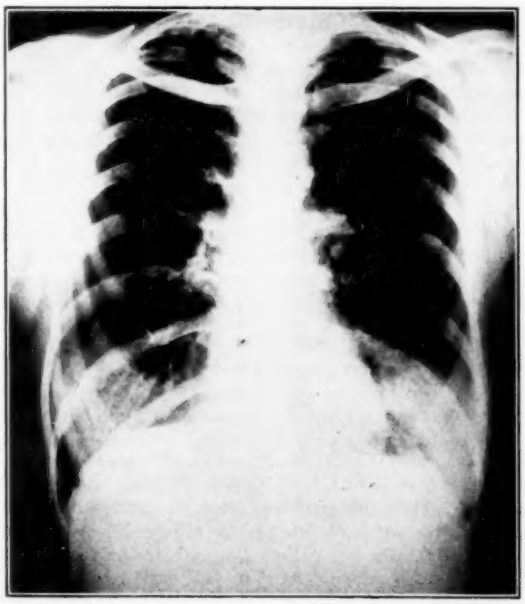

Fig. 2. Case S. S. – Roentgenogram showing left lower lobe pneumonia. Re-examination 10 days later demonstrated complete resolution.

from 8,000 to 11,000, which subsequently fell to lower levels. Seven patients with pneumonia remained leukopenic, with counts ranging from 3,000 to 6,400.

Necropsies were secured in 9 cases. Sections were reviewed by Dr. A. Valdes-Dapena, Director of Laboratories at the Graduate Hospital. Patchy pneumonia was observed in 8 cases, and pulmonary edema in 1. Special search for arterial changes similar to those found in the spleen, and for hematoxylin bodies, failed to demonstrate these characteristic lesions. No other specific changes indicative of disseminated lupus were recognized in the lung sections.

Of special interest were three groups of cases, the first manifesting a pattern characterized by recurrent pneumonias, the second showing lesions which simulated tuberculosis, and the third group having symptoms which were predominantly respiratory. The following histories illustrate instances of these types:

Case Reports. RECURRENT PNEUMONIA. *Case 1.* L. S., a 41-year-old colored female, was admitted to Philadelphia General Hospital on May 26, 1950, with a three-year history of facial rash. Cough, chills and fever had developed four weeks earlier. Roentgenray examination on admission revealed pneumonitis in the right lower lobe. The leukocyte count was 8,300. She continued febrile. The chest film on June 30, 1950, revealed pneumonitis in the right upper lobe. On July 31, 1950, the lung fields were clear. She was discharged on August 16, 1950, and readmitted on September 5, 1950, for ACTH therapy. A film on September 11, 1950, revealed patchy infiltration in the right upper lobe.

LESIONS SIMULATING TUBERCULOSIS. *Case 2.* E. J., a 26-year-old colored female, was admitted to Philadelphia General Hospital on September 20, 1949, with pericarditis and bilateral basal pneumonia. The tuberculin test was negative. She gave a history of having been examined at Phipps Institute in 1943 because of contact with tuberculosis. At that time, the tuberculin test was positive (3 + to .00002 mg. P.P.D.) and chest film examination was negative. A diagnosis of tuberculous pericarditis was made and streptomycin therapy instituted. She was discharged improved on December 16, 1949, but was readmitted October 18, 1950, with arthritis and prolonged fever. L. E. cells were demonstrated. Chest films on October 21 and November 30, 1950, were negative. A film on January 12, 1951, showed right lower lobe pneumonia. Death occurred on April 18, 1951. Necropsy was not secured.

Case 3. J. B., a 30-year-old colored male, was admitted to Philadelphia General Hospital on August 16, 1949, with a three-year history of arthritis, fever and chest pains. Chest film showed scanty infiltration in the left upper lobe. The patient was discharged with the diagnoses of disseminated lupus and minimal inactive tuberculosis. In November, 1949, he was readmitted with diffuse bilateral patchy pneumonia, and died on January 17, 1950. Necropsy revealed lobar pneumonia, right lower lobe, and characteristic renal lesions of lupus. No evidence of tuberculosis was found.

PREDOMINANTLY RESPIRATORY MANIFESTATIONS. *Case 4.* E. P., a 57-year-old colored male, was admitted to the urological service of Graduate Hospital on August 20, 1951, because of back pain, hematuria and fever of two weeks' duration. Chest film on admission was negative. Hematuria subsided, but the fever persisted and right pleuritic pain developed. A roentgenogram on August 29, 1951, revealed pleural effusion. Urological studies having proved negative, the patient was transferred to the medical service for further study. The tuberculin test was 2 + to .005 mg. P.P.D. Pleural fluid was negative on bacteriological study. A trial of streptomycin and PAS failed to influence the fever or accumulation of pleural fluid. Disseminated lupus was considered, because of leukopenia, hyperglobulinemia and the recent hematuria. L. E. cells were demonstrated in the marrow on two occasions.

Case 5. E. M., a 33-year-old colored female, was admitted to the chest diagnostic ward at Philadelphia General Hospital on August 24, 1951, with cough of three months' duration, chest pain, fever, and weight loss. She had had pneumonia in each of the three preceding winters. Clinical and roentgenographic evidence indicated bilateral basal pneumonitis, with pleuritis on the left. A lymph node biopsy was negative, as were sputum smears. The tuberculin test was negative, which was thought to represent toxic energy. Streptomycin and PAS therapy was instituted on September 12, 1951, without improvement. Serum globulin was 6.8 gm., and the leukocyte count 8,150. Lupus cells were sought

and demonstrated in the marrow. A consultant advised against ACTH therapy, because he doubted the diagnosis of lupus. Death occurred on October 21, 1951. Necropsy revealed focal necrotizing pneumonia and typical fibrinoid lesions in the kidney, characteristic of disseminated lupus.

Discussion. Osler[11], in an early description of disseminated lupus, noted the frequency of pneumonia and remarked on the likelihood "that the recurring skin lesions, the pleuropneumonia, the phlebitis, the general glandular enlargement, and the fatal nephritis were due to one and the same poison".

In recent years, roentgenological studies have been concerned with the subpleural[14] or diffuse pulmonary changes that occasionally accompany disseminated lupus; the latter lesions, like those of the other collagen disorders, are considered by some authors to be of vascular origin[3], and by others to be perivascular, of allergic etiology[13]. Pathological studies, on the other hand, have emphasized the frequency of nonspecific pneumonias in the terminal stages of the disease[4]. Rather infrequently, specific pulmonary changes consisting of interstitial pneumonitis and atelectasis have been described[2,6,12].

Tumulty and Harvey's study[15] of 32 cases of disseminated lupus seen at the Johns Hopkins Hospital revealed that pulmonary disease was a frequent concomitant. Pneumonia occurred in 13 patients, tuberculosis in 2, and there were single instances of abscess, infarct and empyema. In addition, there were 3 patients who, on pathological study, were found to have "specific" pulmonary lesions. Two had diffuse patchy collagenous lesions, with changes similar to those noted in the kidneys, while another had a pneumonia which, characterized by mononuclear infiltration, resembled rheumatic pneumonitis.

Hodges[8] recently described a patient with disseminated lupus who had 8 episodes of what appeared roentgenologically like early lobar pneumonia within a 4-year period. Although the pulmonary aspects have not been emphasized by Klemperer, Baehr and their associates[1,9], one of their comments deserves quotation: "Postmortem observations do not properly reflect the remarkable clinical manifestations of pulmonary involvement in this disease; the long bouts of waxing and waning migrating bronchopneumonia"[10].

It appears a reasonable conclusion from these reports, as well as from our observations on 22 patients, that pulmonary involvement is extraordinarily frequent in disseminated lupus. However, the diffuse perivascular lesions which have been described as characteristic of the collagen disorders are only occasionally observed in disseminated lupus; they were noted roentgenologically in but one patient in the present study. Specific pulmonary lesions are uncommon on pathological examination; they were not observed at necropsy in 9 cases at Philadelphia General and Graduate Hospitals. Similarly, large pleural effusions resulting from serositis of lupus appear to be relatively uncommon, having been noted in only 2 of the patients in the present study.

By far the most common pulmonary manifestation of disseminated lupus is pneumonia, either lobar or patchy in distribution, presumably bacterial in etiology, and in most instances responding in usual fashion to antibiotic therapy. A striking feature, indicative of special susceptibility to pneumonia, is the recurrent and migratory character of the infections, noted in 3 of our patients, and alluded to by Hodges[8] and by Klemperer[10].

The cause for the marked susceptibility of the lupus patient to pneumonia is not clear. It may be the result of the general depression of resistance to infection which characterizes this disease,

but local factors are probably also involved. Bagenstoss[2] has observed mucinous interstitial edema of the alveolar walls, which he suggests may be responsible for the interstitial pneumonitis that is observed in this disease, but he cautions that this type of pneumonitis is to be distinguished from ordinary pyogenic and fibrinous types of bronchopneumonia. One may suspect that some alteration of bronchial or pulmonary structure is likewise responsible for the extraordinary frequency of bacterial pneumonias in disseminated lupus erythematosus.

Until recently, the diagnosis of disseminated lupus erythematosus was rarely considered, unless a butterfly malar rash, polyserositis, renal involvement, endocarditis, leukopenia, and elevated serum globulins were present. The development of a useful diagnostic test, the L. E. phenomenon, now permits recognition of the disease in many instances in which the classical manifestations are lacking. Application of the L. E. test, moreover, has resulted in an expanded concept of disseminated lupus; it is evidently a more widespread disease than has hitherto been suspected. Patients with a variety of neurological, hematological and gastrointestinal manifestations[5] have been found to exhibit the L. E. cell phenomenon. It has been suggested that disseminated lupus may first manifest itself by such syndromes as epilepsy and hypersplenism[7]. It appears justifiable to suggest that another mode of onset may be with respiratory symptoms. In many instances, the pulmonary manifestations are overshadowed by those of the systemic illness, but occasionally, as in 2 of the patients we have described, respiratory symptoms may dominate the clinical picture. This observation is of considerable importance, for it demonstrates that in pulmonary or pleural diseases of obscure etiology the diagnosis of disseminated lupus requires consideration.

Conclusions and Summary. (1) Pulmonary involvement is so common in disseminated lupus that it cannot be considered coincidental.

(2) Specific pulmonary lesions, comprising either disseminated perivascular changes or chronic interstitial pneumonia, and massive pleural effusion are relatively infrequent.

(3) The most common manifestation is a non-specific pneumonia, which occurs not only as a terminal event, but is frequently a recurrent or migrating process.

(4) Disseminated lupus may occasionally present with predominantly respiratory manifestations. A search for the L. E. phenomenon should be made in patients with recurrent pneumonias, infiltrations or pleurisies of uncertain etiology.

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INTERSTITIAL PNEUMONIA AND FOCAL MYOCARDITIS IN POLIOMYELITIS

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and

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The infectious character of poliomyelitis was established in 1890 by Medin[12], whose name, in combination with that of Heine, is used in many countries for the designation of the disease. In addition to clinical and epidemiological observations he presented in detail the pathological picture, including even the encephalitic lesions. Despite the absence of bacteria in the tissues, Medin considered the disease to be of an infectious nature, largely on the basis of the gross visceral pathology in his cases. He observed cloudy swelling of the myocardium, liver, and kidneys, and hyperplasia of lymphoid tissue in the spleen, lymph nodes, Peyer's patches, and solitary follicles of the intestine "as seen in severe infectious diseases." Medin considered that the disease involved not only the gray matter of the spinal cord but the whole organism.

This broad concept was later largely disregarded and until recently poliomyelitis was considered to be a disease caused by a strictly neurotropic virus. As a result, little attention was paid to visceral changes. In the past 10 years, since acute focal myocarditis in poliomyelitis was described by Larson[10] and by Saphir and Wile[16], the attention of a number of investigators has been directed to the pathological changes in the heart[3,11,13,15,17] and electrocardiographic findings[1,2,4,5,14].

The occurrence of interstitial pneumonia in poliomyelitis was reported in 1945 by Saphir[15], who found it in 6 of 17 necropsy cases. Gefter *et al.*[5] found 3 cases of interstitial pneumonia in 6 necropsies of poliomyelitis. Since the number of cases in these studies was small and did not permit any conclusion as to the incidence of interstitial pneumonia in poliomyelitis, we undertook to investigate the occurrence of this finding in the large necropsy material of the Willard Parker Hospital. While reviewing the slides of the lungs, we re-examined the sections of the hearts which had been investigated by one of us (V. B. D.)[3]. The material which has since accumulated was added so as to bring up-to-date the statistical data on focal myocarditis in our necropsy cases.

Material. The total number of complete necropsies in cases of poliomyelitis was 140. Some of this material could not be used, however. Cases in which death had occurred more than a month after the onset of the disease were omitted since they were not representative of the acute stage of poliomyelitis. In some cases the old slides from the files had faded and were unsatisfactory. We decided also to omit from the study those lungs which showed evidence of tuberculosis and those from cases in which the patient had had pneumonia shortly before poliomyelitis, since these conditions could have produced interstitial pulmonary changes.

Hearts which showed rheumatic myocardial lesions were listed as negative for acute focal myocarditis.

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INTERSTITIAL PNEUMONIA. Lungs in which interstitial pneumonia was found microscopically were usually well aerated and, on gross inspection, did not suggest the presence of an inflammatory process.

Our criteria for the microscopic diagnosis coincided with those of Saphir[15]. The bronchial mucosa showed a predominantly lymphocytic infiltration and the bronchial lumen did not contain many polymorphonuclears. The peribronchial tissues showed infiltration with lymphocytes and some plasma cells, extending out into the walls of the adjacent alveoli. The infiltrates were heaviest in the walls nearest the bronchi and gradually diminished in severity in more distant alveoli (Fig. 1). Thickening and greater cellularity of alveolar walls in areas of atelectasis were not considered to be of an inflammatory nature. The lumina of the thick-walled alveoli were either free of inflammatory exudate (Fig. 2) or contained some macrophages, a small number of polymorphonuclears, some edema fluid, and, occasionally, a few strands of fibrin. This process could be observed in one or several lobes in a given case. The remaining lobes could either be free of pneumonia or show a lobular or hypostatic pneumonia.

Microscopic evidence of some form of pneumonia was found in 62 of 121 cases (an incidence of 51%). Interstitial pneumonia was seen in 31 cases (25.6% of all cases) in one or more lobes. It was the only pneumonic lesion in 18 cases (14.9%). In an additional 13 cases interstitial pneumonia was present in one or more lobes, while some other form of pneumonic process was seen in other lobes, usually the lower.

None of our cases showed a hyaline membrane lining the alveoli. Gross mucous plugs were not encountered in large bronchi, possibly because of postural drainage and frequent suctioning. Microscopic plugs filling the lumen of small and medium sized bronchi (Fig. 3), were observed, however, in 12 cases. They were seen in occasional bronchi in 3 of the cases of interstitial pneumonia, as well as in cases with lobular pneumonia or with no inflammatory lesion at all. The mucosa of some of the bronchi containing mucous plugs showed an unusually large number of goblet cells. This finding was especially prominent in cases with evidence of aspiration of gastric contents in the form of bile-stained material, or of brown-tinged red blood cells.

TABLE 1.–PNEUMONIA IN 121 CASES OF ACUTE POLIOMYELITIS

Pneumonia (all forms)	62 cases	(51%)
Interstitial pneumonia (total cases)	31 „	(25.6%)
Interstitial pneumonia alone	18 „	
Interstitial pneumonia with another form of pneumonia elsewhere	13 „	

MYOCARDITIS. Foci of myocarditis, in the order of frequency, were found in the interventricular septum, in the posterior papillary muscle of the left ventricle, in the posterior wall of the left ventricle, or in the walls of the auricles. The inflammatory foci consisted of cellular collections in the interfascicular connective tissue or within the muscle bundles. The predominating cells in the infiltrates were histiocytes with oval or folded nuclei. Some histiocytes with elongated nuclei were seen clinging to individual necrotic muscle fibers. Polymorphonuclears were present in some foci, especially in the proximity of hemorrhages. Lymphocytes were less frequently encountered in our material, possibly because all our cases were

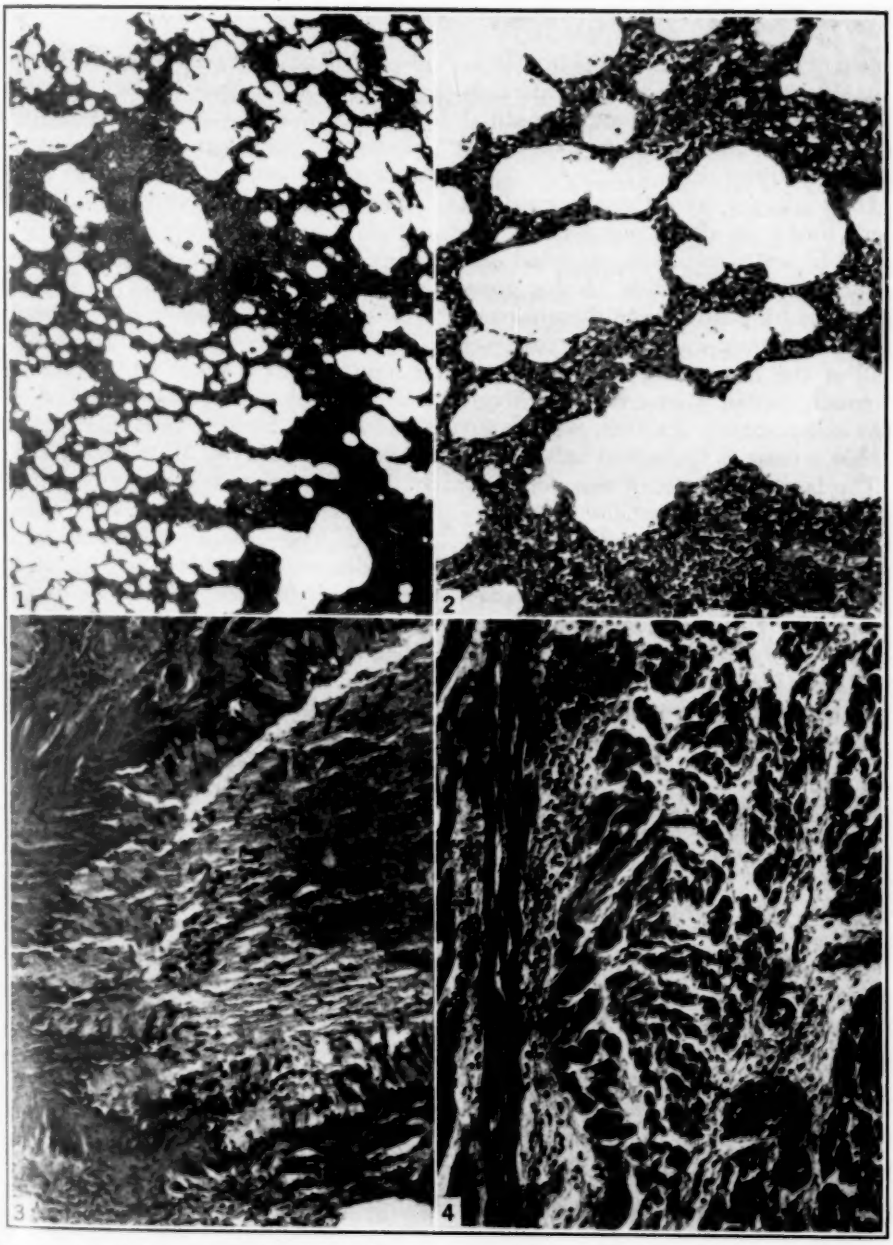

Fig. 1.—INTERSTITIAL PNEUMONIA. Peribronchial infiltration extending into the walls of alveoli. Hematoxylin and eosin. × 25.

Fig. 2.—INTERSTITIAL PNEUMONIA. Infiltration of alveolar walls with mononuclear cells. No exudate within the alveoli. Hematoxylin and eosin. × 65.

Fig. 3.—BRONCHUS FROM A CASE OF INTERSTITIAL PNEUMONIA. Active secretion of mucus by goblet cells. The lumen is filled with mucus and partly digested red blood cells (aspirated "coffee ground material"). Hematoxylin and eosin. × 65.

Fig. 4.—FOCAL MYOCARDITIS. Mononuclear infiltrates and congested venules in edematous interstitial tissue. × 100.

recent (Table 2). According to Spain *et al.*[17] lymphocytes are prevalent in cases of longer duration. Interstitial edema was quite marked in some cases of myocarditis (Fig. 4).

Hemorrhages into the myocardium were found in about one half of the cases. In addition to subepicardial and subendocardial petechiae, larger gross hemorrhages were seen in the interventricular septum and in the posterior wall of the left ventricle. In one case a small recent hemorrhage, without any inflammatory reaction, was found within a cusp of the mitral valve.

The largest number of cases of myocarditis was seen in patients dying between the third and the fifth days from the onset of the disease. This was true of the older[3], as well as of the newer series. The combined data on the 29 cases (16 from the older study, 13 new cases) are presented in Table 2.

No electrocardiographic studies were done on any of these patients.

TABLE 2.—DURATION OF POLIOMYELITIS IN 29 CASES OF FOCAL MYOCARDITIS

Days	*Cases*
2	3
3	5
4	7
5	9
6	2
8	1
10	2
	29

In calculating the incidence of myocarditis we decided to confine the study to those cases from which multiple blocks of myocardium had been taken, and to omit those in which only one section of heart tissue was available since the chance of missing focal myocarditis under such conditions is too great. Of the 120 heart specimens, multiple blocks of myocardium were available in 73 cases. Focal myocarditis was present in 24 of these (32.87%).

The occurrence of focal myocarditis was not related to the presence or absence of pneumonia (Table 3).

Discussion. The occurrence of interstitial pneumonia had escaped the notice of investigators, even when looked for, until the work of Saphir[15] who observed 6 such lesions amongst 17 cases of poliomyelitis. In our study of lungs from 121 cases, which includes the material previously reviewed by Landon and Smith[9], interstitial pneumonia was seen in 31 cases (25.6%). In 18 of these it was the only inflammatory lesion in the lungs; in 13 others interstitial pneumonia was observed in one or more lobes, while bronchopneumonia or hypostatic pneumonia of various degrees of severity was present in other lobes.

Since interstitial pneumonia occurs in a number of virus diseases, Saphir[15] suggested that the virus of poliomyelitis could be the etiological factor in the development of interstitial pneumonia in that disease. This supposition will require experimental support. The probability of viral etiology of myocarditis in poliomyelitis has been suggested by several authors[3,11,17]. This premise received greater justification since the recovery of the poliomyelitis virus from the hearts in cases of that disease and by experimental production of myocarditis in monkeys after infection with poliomyelitis[6,7]. Besides the myocardium, the paralyzed skeletal muscle was found to contain the virus also on one occasion[8]. These experimental investigations lend support to Medin's concept of poliomyelitis as a general infection. Since viremia is infrequent in poliomyelitis[19], or possibly occurs in the preclinical stage of the disease, as suggested by Jungeblut[6], isolation of the virus from visceral sources means fixation of the virus in such tissues, making the etiological connection of

the virus and the lesion plausible. If the time comes when the virus of poliomyelitis can be found in the lungs, the concept of the viral origin of interstitial pneumonia will gain support.

Recent experimental work, however, makes possible another explanation for the development of interstitial pneumonia in some cases of poliomyelitis. Teabeaut[18], by introducing filtered human gastric contents into the trachea of rabbits, produced desquamation of bronchial epithelium, thickening of the alveolar septa with mononuclear and polymorphonuclear cells, and the appearance of edema fluid and some polymorphonuclears in the alveolar lumen. These changes, which occurred as early as on the second day after the injection of the gastric contents, presented the characteristics of an interstitial pneumonia. In bulbar poliomyelitis there exists a situation very similar to that induced in these experiments since regurgitated gastric contents can enter the bronchial system even when the best postural drainage and instrumental aspirations are employed, as has been shown in sections of lungs from such cases. There is a possibility, therefore, of a non-viral origin for the interstitial pneumonia found in some cases of poliomyelitis.

Summary. Interstitial pneumonia was found in 25.6% of fatal cases of poliomyelitis. It occurred either as the only pneumonic process in the lungs or in combination with some other form of pneumonia.

Acute focal myocarditis was observed in 32.9% of 73 cases of poliomyelitis in which multiple sections of myocardium were available.

Further experimental work will be required to establish the viral etiology of interstitial pneumonia in poliomyelitis. The possibility that such pneumonia may be due to the aspiration of regurgitated gastric contents is discussed.

TABLE 3

Findings in the Lungs	*Myocarditis*
Severe lobular pneumonia	3
Minimal, microscopic lobular pneumonia	4
Hypostatic pneumonia (or hemorrhagic infarct)	5
Interstitial pneumonia	4
No pneumonia	14
	29

ACKNOWLEDGMENT: We are indebted to Mr. Julius Weber for most of the photographs.

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THE MANAGEMENT OF THE SHOCK IN MYOCARDIAL INFARCTION WITH l-NOREPINEPHRINE

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During the past 18 months, l-norepinephrine has been used in the treatment of peripheral vascular collapse in 50 patients. In this group, 13 had developed the shock syndrome following an acute myocardial infarction proven by electrocardiogram. It is the purpose of this paper to relate our experience at the Rhode Island Hospital with l-norepinephrine in the management of cardiogenic shock secondary to acute myocardial infarction. Our results in the other 37 cases will be the subject of a later report. The rationale of this form of therapy is related to its ability to increase vascular tonus at the time when many hormonal and toxic factors may be exerting a vasodepressive action. In addition, the importance of maintaining adequate blood supply to the heart[3,17,25], brain[18] and kidney[13] is apparent. Finally, arterial hypotension is often the earliest constant feature of the shock state in acute myocardial infarction, and the use of a pressor amine at this time would represent a rational therapeutic approach.

Methods and Materials. Solutions were prepared for intravenous administration by adding 4.0 mg. of Levophed to 1000 cc. of 5% dextrose in water. The rate of administration was determined by the pressor response obtained. Once a desired effect was produced, the infusion was allowed to run at the optimum rate, with frequent checking of the blood pressure and pulse. In addition toxic reactions were constantly looked for and recorded. These have been described elsewhere in the literature[9,12,24]. The only patients included in this study were those whose systolic blood pressure had fallen to less than 80 mm. of Hg following an acute myocardial infarction proven unequivocally by electrocardiogram. Likewise no attempt was made to employ other pressor amines or blood transfusion, though it is realized that a combination of agents may be of benefit in the management of this syndrome in certain instances.

Results. The results of our experience in the treatment of shock accompanying myocardial infarction are summarized in Table 1. Eleven patients were male and 2 were female. The youngest patient in the group was 57 years of age, and the oldest 80. The average age was 66. The blood pressure was unobtainable in 11 patients prior to therapy. The other 2 had initial blood pressures of 70/50 and 60/0 respectively. Only one of these patients had sustained a previous myocardial infarction and in no instance was ventricular tachycardia encountered.

In 4 cases it was felt that l-norepinephrine was administered with life-saving results. Two of these patients, M.G. and W.Q., subsequently made uneventful recoveries. The effect of therapy in patient M.G. is shown in Fig. 1. It demonstrates the rapid action of Levophed and the potentiation of its effect by increasing the rate of infusion. The other 2 patients, E.M. and

TABLE 1.—RESULTS OF TREATMENT

Name	*Age*	*Sex*	*Duration Shock Before Treatment*	*B.P. Before Treatment*	*Pulse*	*Amount Drug Given*	*Duration Treatment*	*Complications*	*Response*
J. M.	62	M	undetermined	0/0	90	less 1 mg. 20 drops/min.	1 and ½ hours.	none	None; pt. expired immediately
A. R.	75	F	6 hours	0/0	140	4 mg. at 20 drops/min.	7 hours	none	B.P. rose to 100/60 after .8 mg. Levophed. Shock state returned and pt. expired in 24 hours.
I. B.	76	F	undetermined	0 0	130	4 mg. at 20 drops/min.	Several hours	none	None; pt. expired on 3rd hospital day.
G. C.	58	M	undetermined	0 0	96	4 mg. at 20 drops/min.	5 hours	none	None
E. M.	72	M	12 hours	60/0	110	32 mg. at 20–32 drops per minute	20 hours	none	B.P. rose to 100/65 after 4 mg. Levophed. Pt. died on 41st hospital day of pulmonary infarction.
G. C.	55	M	undetermined	0/0	0	4 mg. at 15 drops/min.	3 hours	pulmonary edema	B.P. rose to 100/70 after 1.5 mg. Levophed. Shock state returned; pt. died in 3 hours.
A. R.	65	F	1 hour	0/0	96	20 mg. at 24 drops/min.	intermittently over period of 3 days	none	B.P. rose to 124/60 after 2 mg. Levophed. B. P. stabilized. pt. died on 18th hospital day of cerebral embolism.
W. D.	60	M	1 hour	0 0	70	8 mg. at 60 drops/min.	12 hours intermittently	none	B.P. rose to 124/60 after 1.0 mg. Levophed. Pt. expired on 2nd hospital day.
F. B.	80	M	undetermined	0 0	0	4 mg. at 30 drops/min.	16 hours	none	B.P. rose to 100/70 after .4 mg. Levophed. Pt. expired 16 hours after entry.
C. K.	57	M	undetermined	0/0	0	4 mg. at 30 drops/min.	24 hours	none	None; pt. expired suddenly.
W. S.	74	M	undetermined	0 0	43	1.4 mg. at 30 drops/min.	5 hours	pulmonary edema	B.P. rose to 70/64 after 1.4 mg. Levophed. Pt. expired 12 hours after entry.
M. G.	65	M	undetermined	70/50	48	6 mg. at 28 drops/min.	12 hours	none	B.P. rose to 120/72 after .2 mg. Levophed; B. P. stabilized; pt. recovered
W. Q.	68	M	1 hour	0 0	0	8 mg. at 30 drops/min.	12 hours	none	B.P. rose to 120/80 immediately after start of infusion. B.P. stabilized; pt. discharged on 25th hospital day.

A.R., later died from pulmonary infarction and cerebral embolism respectively. The most dramatic response observed in this series was in patient A.R. Before therapy, blood pressure was 0/0, and she was cold, clammy and cyanotic and unresponsive. l-Norepinephrine, 4 mg. in 1000 cc. of 5% dextrose in water, was infused at the rate of 24 drops a minute. Within 5 minutes, her blood pressure was 90/40 and her color much improved. The effect of l-arterenol in this case is illustrated in Fig. 2. These 4 cases are reported below.

Of the remaining 9 patients, an impressive pressor response was obtained in 5 instances. These 5 cases had no obtainable blood pressure prior to administration of Levophed. In each case the systolic blood pressure rose to at least 100 mm. of Hg. The amount of drug necessary to produce a satisfactory response was variable and ranged from 0.4 mg. to 1.5 mg. Four patients showed no response. One of these, I.B., is of particular interest in that she lived for 48 hours without blood pressure and developed changes suggestive of early ante-mortem gangrene. In addition, when it appeared that she was *in extremis*, she was given 4 mg. of Levophed directly intravenously without any effect on blood pressure or pulse rate.

Pulmonary edema was encountered in 2 instances after adminstration of Levophed. Whether this was a result of treatment or a sequela of myocardial infarction could not be determined.

Case Reports. CASE 1. W.L., a 68-year-old white male, was admitted to the hospital on April 30, 1953, because of crushing chest pain of several hours' duration. On examination, temperature was 102°, pulse 130, respiration 30, and blood pressure 114/94. Rales were heard at both lung bases. The heart was enlarged to the left and the sounds were of poor quality. The electrocardiogram was diagnostic of an acute posterior myocardial infarction. On the morning following admission, the patient suddenly went into complete peripheral vascular collapse. No blood pressure or pulse could be obtained. He was given l-norepinephrine and an immediate pressor response was noted. Blood pressure stabilized at 120/80; a total of 8 mg. of l-norepinephrine was given over a 12-hour period at the rate of 30 drops a minute. Improvement was steady and gradual and the patient was discharged on his 25th hospital day.

CASE 2. E.M., a 72-year-old white male, was referred into the hospital on December 23, 1952, by his physician after examinations at home revealed the presence of a shock state with no obtainable blood pressure and a pulse rate of 45. Severe chest pain had been present for many hours. The patient had had 2 previous admissions for myocardial infarction. On entry, he was found to be in peripheral vascular collapse with a blood pressure of 60/0. An electrocardiogram revealed the presence of an acute posterior myocardial infarction. l-Norepinephrine was administered and a satisfactory pressor response was obtained in two hours. Blood pressure then was 100/60. During the next 22 hours, a total of 22 mg. of arterenol was administered at the rate of 20 to 30 drops a minute with good response. The patient did well initially but finally expired on his 41st hospital day. Necropsy revealed a recent myocardial infarct and multiple pulmonary emboli.

CASE 3. A.R., a 65-year-old white female was admitted to the hospital on March 27, 1952, with a chief complaint of chest pain of 4 days' duration. On entry, temperature was 99°, pulse 96, respiration 30, blood pressure 130/80. The heart sounds were feeble, and there were signs of leftsided failure. An electrocardiogram revealed an acute anterior myocardial infarction. Shortly after admission, chest pain recurred and the patient became cyanotic, and dyspneic. Peripheral vascular collapse followed, and neither blood pressure or pulse could be obtained. l-Norepinephrine was given at the rate of 24 drops a minute and a blood pressure of 124/60 was recorded after 2 mg. were administered. A total of 20 mg. were given over a 3-day period. Subsequently the blood pressure stabilized and the patient was doing well until her 18th hospital day when she developed a cerebral vascular accident and expired shortly after.

CASE 4. On October 21, 1952, M.G., a 65-year-old white male, entered the hospital because of crushing chest pain of several hours' duration. On examination, his temperature was 98.6°, pulse 48, respiration 30, and blood pressure 70/50. Heart sounds were of poor

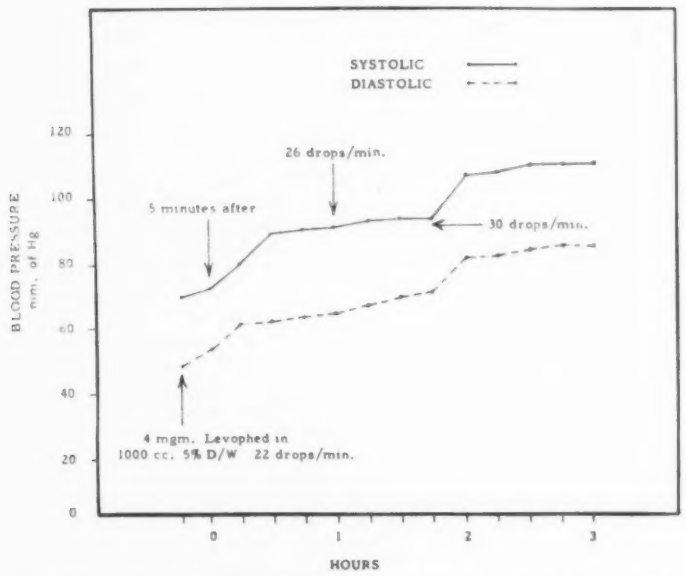

Fig. 1.—Patient M.G. This demonstrates the effect of the rate of infusion of l-norepinephrine on the pressor response.

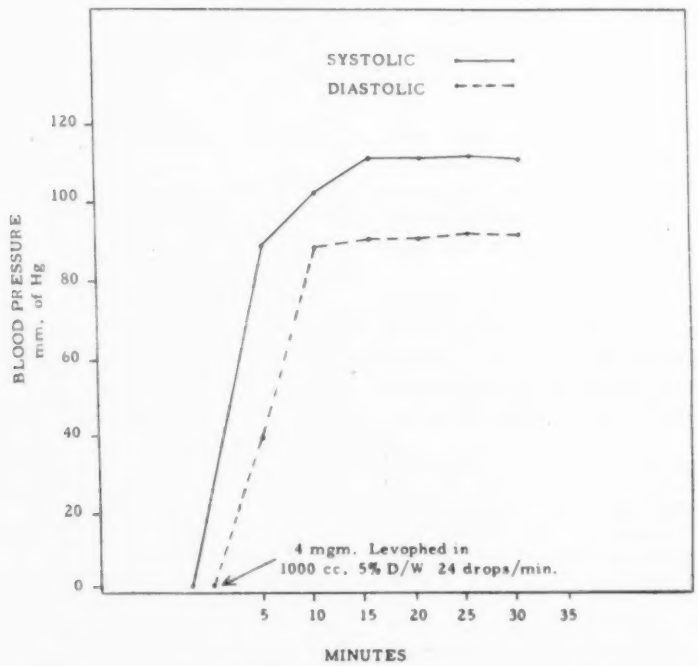

Fig. 2.—Patient A.R. This illustrates the rapid pressor response to l-norepinephrine.

quality; there were no signs of congestive failure. An electrocardiogram was diagnostic of an acute posterior myocardial infarction. l-Norepinephrine 4 mg. in 1000 cc. of 5% dextrose in water was administered at the rate of 24 drops a minute and the blood pressure rose to 92/60 in 20 minutes; subsequently the blood pressure stabilized at 110/70 after a total of 4 mg. of Levophed had been given. His course was complicated by the development of a cerebral vascular accident on his third hospital day from which he recovered partially. He was discharged 3 months later.

Comment. Despite the fact that the shock picture accompanying myocardial infarction has been recognized for over 40 years[11], there still is no unanimity of opinion concerning the pathogenesis and treatment of this form of vascular collapse. One group of investigators[10,21] has maintained that the disorder is the result of "acute forward failure", due to the inability of the heart to provide a normal cardiac output. Others[5] have provided evidence which indicates that the circulatory failure associated with myocardial infarction is similar to the other forms of shock and is characterized by a diminution in venous return to the heart. Harrison[10] and Master[15] have suggested that myocardial infarction may initially induce peripheral collapse via a reflex mechanism. Experimental work in animals lends support to that contention[23]. Recent hemodynamic studies by Freis[6] in man suggests that the initial change after myocardial infarction is a reduction in stroke volume and cardiac output. A series of compensatory mechanisms characterized by intense vasoconstriction and tachycardia appear and produce the clinical picture of shock. A fluid retention syndrome may develop later. Finally, the vasoconstrictory responses may overextend themselves and lead to a state of "irreversibility"[26].

The method of combating post-coronary shock is not yet agreed upon. One school believes that the fall in blood pressure exerts a salutary action[7,22]. Stead and Ebert[21] withdrew 500 and 650 cc. of blood in 2 patients with myocardial infarction with no harmful effects. Corday *et al.*[3] have suggested that a weakened and herniating myocardium may show a prompt return toward normal with addition of blood or plasma. However, Epstein and Relman[4] noted no impressive benefit in 30 patients with the use of blood transfusion with shock following coronary occlusion. More recently, intra-arterial transfusions have gained attention[1,20]. The advantages listed include the use of smaller amounts of blood, better perfusion of the coronary vessels, and increased renal filtration pressure. The results in a small number of cases reported have not been encouraging, and the method is not without danger[2]. Our experience with l-norepinephrine in the treatment of shock complicating myocardial infarction is similar to that of others. Miller and Baker[16] noted partial pressure elevations in 4 of 7 patients with survival in only one case. Kurland and Malach[12] described a significant pressor response in the majority of patients though only 4 of the 17 studied survived. More recently Livesay and Chapman[14] administered l-norepinephrine to 6 patients with peripheral vascular collapse secondary to acute myocardial infarction. A response was noted in 66% of the cases and it proved a lifesaving measure in one instance. Sampson and Zipser[19] have observed 16 patients with shock secondary to myocardial infarction. They believed that the early restitution and maintenance of reasonable levels of blood pressure through the use of l-norepinephrine enhanced the rate of survival and decreased the total mortality for the current illness to 56%. In our series, 2 of the 4 patients who recovered from their shock state were given l-norepinephrine within one hour after the development of peripheral vascular collapse. In an-

other patient who survived, treatment was instituted 3 hours after the appearance of chest pain. However, many patients arrived at the hospital in a state of collapse and the duration of shock prior to admission could not be determined. It would appear then that while l-norepinephrine may induce a satisfactory pressor response in shock of myocardial infarction the mortality rate is not significantly reduced. Perhaps earlier and more vigorous treatment as suggested by some observers[8] and the employment of a combination of many agents will provide a more satisfactory attack on this distressing problem.

Summary. 1. The results of our experience in 13 cases in the management of shock accompanying myocardial infarction with l-norepinephrine are presented.

2. l-norepinephrine was used with lifesaving results in 4 cases. A significant pressor response developed in 5 other patients.

3. The mortality rate of shock accompanying myocardial infarction was not significantly reduced by the use of this drug.

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l-TRIIODOTHYRONINE VERSUS l-THYROXINE
A COMPARISON OF THEIR METABOLIC EFFECTS IN HUMAN MYXEDEMA*†

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During the past five years demonstrations by Laidlaw[7], Taurog and Chaikoff[10], and by Rosenberg[9] had led to the conclusion that thyroxine was the thyroid hormone and was the only iodinated compound in the circulation. Doubt was thrown on this concept when Gross and Leblond[1,2] reported that they had observed on their chromatograms of serum taken from animals to which radiothyroxine had been administered a spot which could not be thyroxine. Gross and Pitt-Rivers[3,4] then identified this as triiodothyronine, synthesized it and assayed it for physiologic effects[5,6]. In rats receiving thiouracil and in myxedematous humans they found this new iodinated compound to be 3 to 5 times as active as l-thyroxine.

The present study was undertaken to compare the total metabolic effects of l-triiodothyronine with those of l-thyroxine in a myxedematous patient. Fortuitously, we were able to compare the effects of these compounds with diiodothyronine.

Method. The patient chosen for this study was a 41-year-old woman who by history and physical examination had a classic Gull's disease with classical confirmatory laboratory findings. On the basis of history it was es-

* This work was supported by an institutional grant from the American Cancer Society, an institutional grant from the Damon Runyon Memorial Fund for Cancer Research, and in part by a Grant-in-Aid from The American Cancer Society. It also received support by a grant from the National Cancer Institute of the U. S. Public Health Service and a contract from the A. E. C. No. A. T. (30-1)-910.

Presented before the Association of American Physicians at Atlantic City, New Jersey, May 5 and 6, 1953.

† The triiodothyronine used in this study was supplied by Smith, Kline & French Laboratories for whom it was prepared by Glaxo Laboratories, Ltd.

timated that she had had myxedema between 5 and 8 years.

The patient was placed in the metabolic unit of our research ward, where she received a repetitive diet, aliquots of which were analyzed as is usual on all metabolic balance studies. All urines and stools were saved for analyses of sodium, potassium, chloride, calcium, phosphorus and nitrogen.

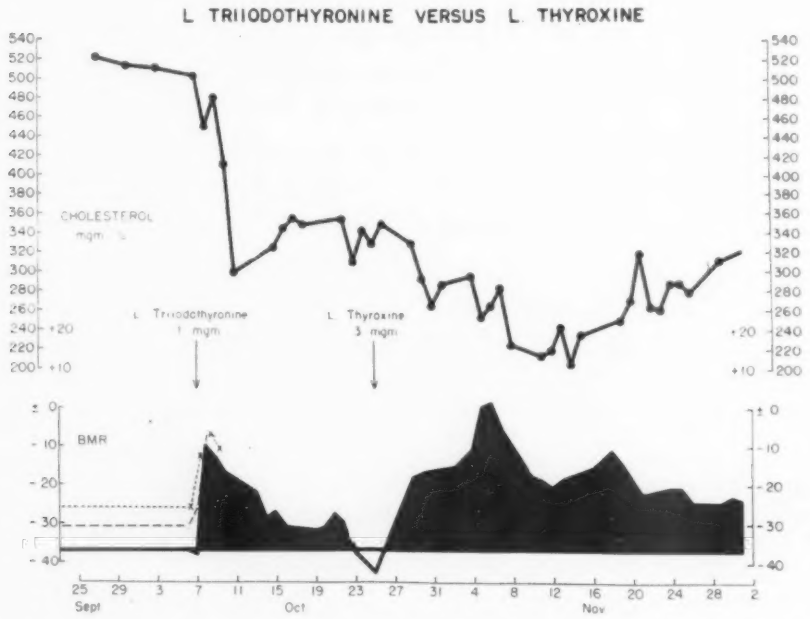

Fig. 1.—The Effects of l-Triiodothyronine and l-Thyroxine on the Basal Metabolic Rate and on the Serum Cholesterol in Myxedema.

The BMR values as plotted following the injection of triiodothyronine represent three-point running averages of the observed values. The solid line before the injection of triiodothyronine represents average pretreatment basal metabolic rates. The broken line represents the average metabolic rate obtained at 11 a.m. and the dotted line represents the average metabolic rate obtained at 4 p.m.

The urine was assayed daily for creatine and creatinine, and at intervals for 17-ketosteroids and pregnanediol. Daily vaginal smears were taken. The serum protein bound iodine and the basal metabolic rate were determined daily, Sundays excepted. During the control periods and for 3 days after administering the test agents, the rate of oxygen consumption was determined each day before lunch and before the evening meal.

Results. The control basal metabolic rates varied between —44% and —32%. They averaged —37%. The metabolic rates obtained at 11 a.m. averaged —32%, while the 4 p.m. metabolic rates varied between —32% and —22% and averaged —27%. The administration of 1 mg. of diiodothyronine (which we thought was triiodothyronine) caused no increase in her metabolic rate nor in her pulse rate.

The intravenous administration of 1 mg. of triiodothyronine at 9 a.m., however, was followed by very significant changes. The metabolic rate at 4 p.m. had risen from an average of —27% to —13%. The following morning her basal metabolic rate was —10%. Thereafter, there was observed a rather rapid return to the pretreatment level in 9

days with a subsequent maximal fall in 16 days (Fig. 1).

l-Thyroxine was administered intravenously in a dose of 3 mg. a dose chosen because of the observations indicating that triiodothyronine is three to five times as active as l-thyroxine. The 4 p.m. metabolic rate did not show any significant increase over the control value. However, the BMR of the next morning had risen to —26%. Within 8 days, the fasting BMR had risen to the level observed 24 hours after administering triiodothyronine. The maximum BMR level was observed at 11 days. Twenty-six days later it still had not reached the pretreatment level. By measuring the area under each of these BMR curves, it becomes quite obvious that the response to thyroxine is between 3 and 4 times greater than that to triiodothyronine. The major difference seems to be in the speed with which this occurs. The triiodothyronine exerts its action promptly, whereas the thyroxine has a slow and prolonged effect.

The serum cholesterols which before treatment had varied between 500 and 520 mg. per 100 cc. fell in 4 days to 300 mg. following the administration of triiodothyronine and then rose gradually to 350 mg., from which level it fell to 230 mg. within 18 days of administering 3 mg. of thyroxine (See Fig. 1).

The diiodothyronine had no effect on nitrogen balance, but did cause a minimal increase in urinary phosphorus. The triiodothyronine produced a prompt increase in urinary nitrogen and phosphorus. Though the total urinary nitrogen following the administration of 3 mg. of thyroxine was approximately the same as it was following the administration of 1 mg. of triiodothyronine, this metabolic effect was slower in developing and lasted longer. The phosphorus excretion following the administration of thyroxine was likewise about the same as that which occurred following the triiodothyronine, but it also was slower in developing and lasted longer. There was no significant effect of either agent on the excretion of calcium. (Fig. 2.) It is of interest that the urinary phosphorus following each of these agents was greater than that expected on the basis of nitrogen and calcium excretion. This is not a new observation, but its mechanism is not clear. Since there also occurred a rise in serum phosphorus, one cannot attribute it to a renal effect. It is possible that the so-called "deposit protein" stored in myxedema contains large amounts of phosphorus, or that the phosphorus was derived from phospholipids which unfortunately were not measured in this study.

By following the creatine excreted after triiodothyronine, it is possible to explain part of the extra phosphorus on the basis of breakdown and excretion of phosphocreatine. (Fig. 3.) Following the thyroxine the discrepancy in actual phosphorus as compared with theoretical phosphorus is less marked, whereas the creatinuria was considerably greater. Thus we are unable to explain the discrepancy with the data that we have. It may represent phosphorus made available by an increased breakdown of ATP or a depression in the formation of high energy phosphate bonds as has been shown by Lardy[8] in *in vitro* studies.

It is of interest that this patient who had been amenorrheic for 4 years and during the control period had shown no significant vaginal cornification, did develop considerable vaginal cornification within 9 days of administering triiodothyronine, and finally had an ovulatory menstrual period after the maximum effect had been obtained from thyroxine. (See Fig. 3).

In this study we failed to observe any effects of either of these agents on the excretion of sodium, chloride or potassium. This is surprising in view

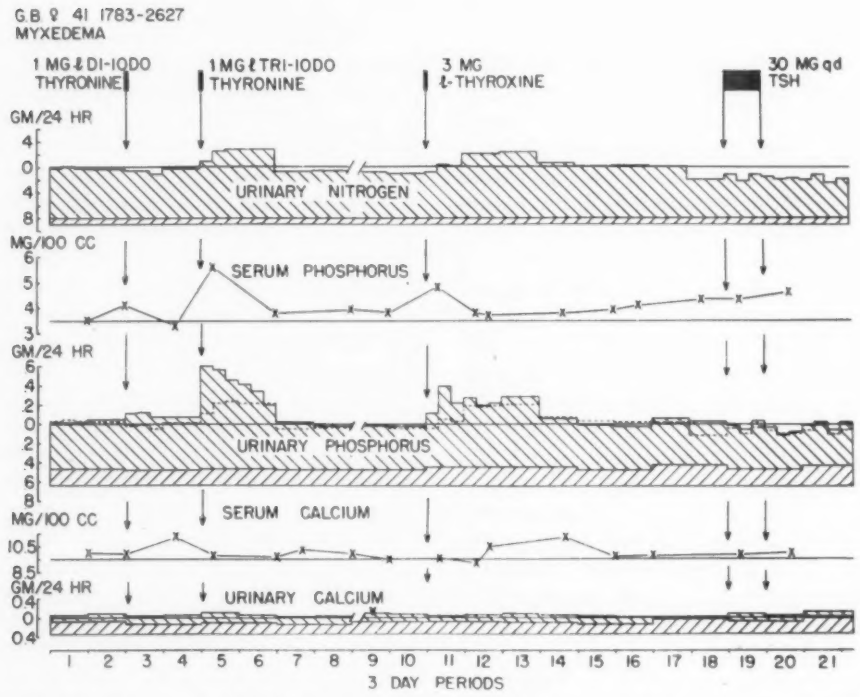

Fig. 2.—The Effects of l-Diiodothyronine, l-Triiodothyronine and l-Thyroxine on the Output of Nitrogen, Phosphorus and Calcium in a Myxedematous Patient Maintained on a Constant Diet.

The intake is plotted below the zero line, and the fecal excretion just above the base line with the urinary excretion above.

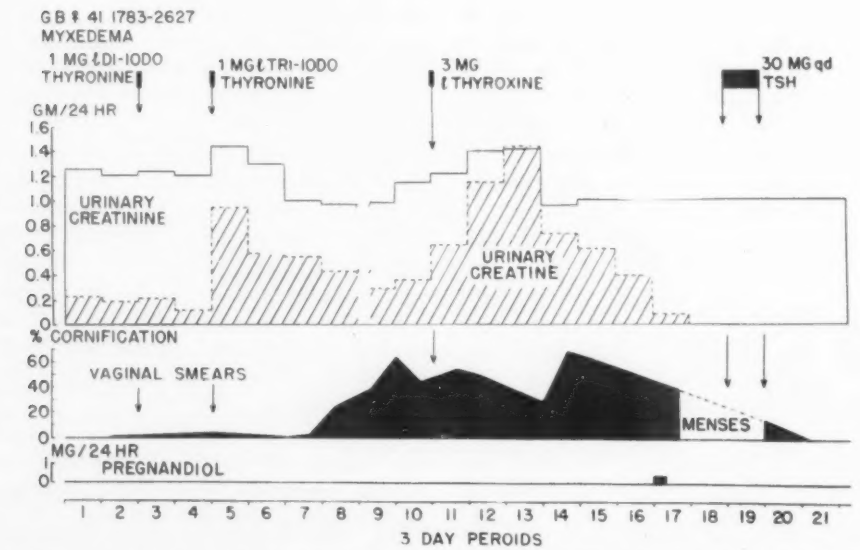

Fig. 3.—The Effects of l-Diiodothyronine, l-Triiodothyronine and l-Thyroxine on the Urinary Excretion of Creatine and on the Vaginal Smears and on the Urinary Pregnanediol.

of the fact that the patient lost approximately 2.0 kilograms after both thyroxine and triiodothyronine. The increase in the levels of sodium, and chloride in the serum suggests that this fluid was lost largely without electrolytes and the patient's extracellular fluid became slightly more hypertonic (Fig. 4).

probably was too early for the patient completely to restore her body stores, normal and abnormal, we are not justified in quantitating the effects of thyroxine against those of triiodothyronine on the excretion of metabolic products. However, notwithstanding these limitations, it appears that in this particular patient triiodothyronine is

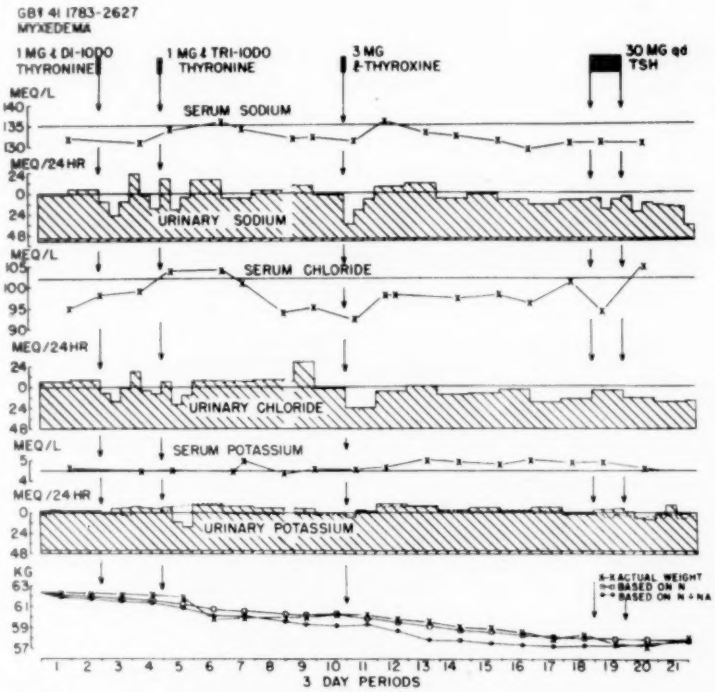

Fig. 4—The Effects of l-Diiodothyronine, l-Triiodothyronine and l-Thyroxine on the Output of Sodium, Chloride and Potassium and on the Actual and Theoretical Body Weights. The values are plotted in a fashion similar to those in Fig. 2.

The urinary excretion of uric acid and of creatinine was likewise measured before, during and after thyroxine and triiodothyronine. There was no change in the excretion of either of these substances after either of the injections.

Since the thyroxine was administered when the patient's BMR had returned to its lowest level, but at a time which

not much more active than thyroxine. Indeed from these observations 3 mg. of l-thyroxine exerted between 3 and 4 times the effect of 1 mg. of triiodothyronine on the total BMR, and about the same effect as triiodothyronine on both the nitrogen and phosphorus excretion. On the excretion of creatine, 1 mg. of triiodothyronine was only about one-third to one-fourth as

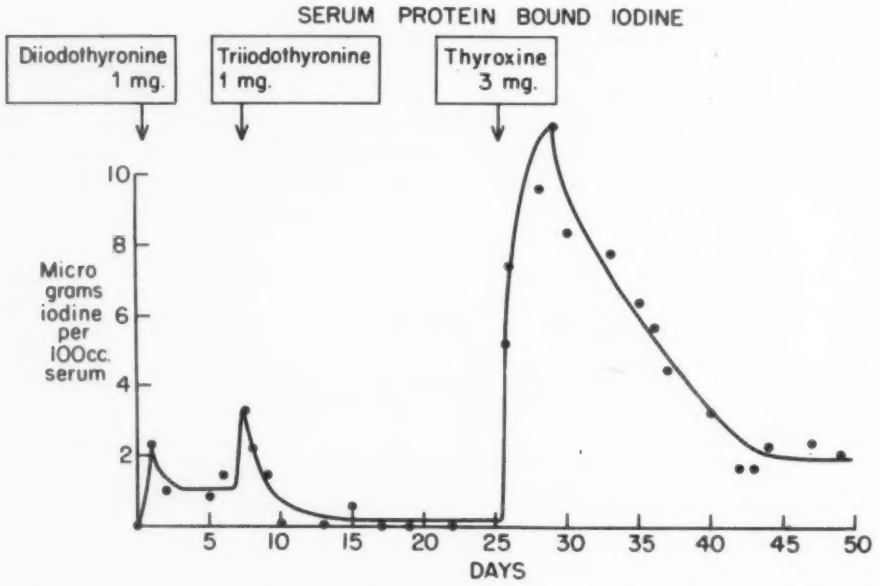

Fig. 5.—The Serum Protein Bound Iodine Levels following the Administration of l-Diiodothyronine, l-Triiodothyronine and l-Thyroxine.

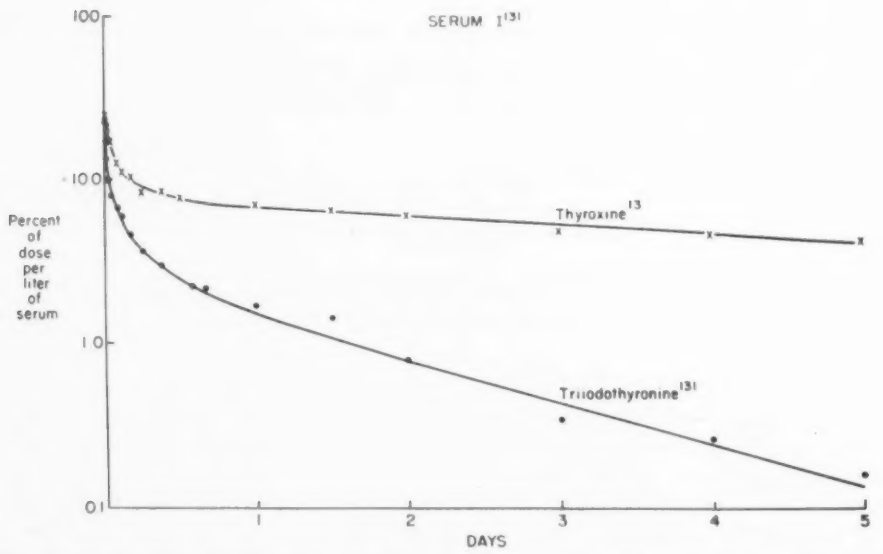

Fig. 6.—Radioactivity in the Serum following the Intravenous Administration in Athyreotic Patients maintained on Desiccated Thyroid of l-Thyroxine and l-Triiodothyronine labeled with I-131.

active as was thyroxine in a dose of 3 mg. The major and significant differences were in the speed with which these metabolic effects occurred. In all of the metabolic effects observed, triiodothyronine exerted its maximum effect almost immediately, whereas the effects of thyroxine were slow and prolonged. No qualitative differences in the effect of these compounds on a wide variety of indices is apparent.

If one considers the fate of these hormonal preparations, one might see a reason for the differences in speed of action. The serum protein-bound iodine following the administration of triiodothyronine rose promptly and had practically disappeared after 36 hours. Following the administration of l-thyroxine, the PBI rose considerably higher and fell almost to the pretreatment level in 18 days. (Fig. 5).

This has been demonstrated more precisely by following the disappearance rates of triiodothyronine and of thyroxine labeled with I-131 in athyreotic euthyroid humans. The half life of triiodothyronine we have found to be two and a half days, that of thyroxine to be between 6 and 12 days. Another difference that we have noted is that following the administration of labeled thyroxine a pool of radioactivity is readily demonstrable for some time over the liver. Following the administration of labeled triiodothyronine in the one patient that we have studied, the radioactivity disappeared very promptly from the liver area. (Fig. 6).

Summary. The metabolic effects of diiodothyronine, triiodothyronine and tetraiodothyronine have been compared in a patient with classic myxedema.

Diiodothyronine in the dose of 1 mg. had no significant effect on any of the indices measured.

Triiodothyronine exerted a prompt but short-lived increase in the BMR, and in the excretion of nitrogen, phosphorus and creatine.

Thyroxine exerted a slow and prolonged effect on the same indices.

If one disregards time of action, there were no qualitative differences between these two agents.

Quantitatively, on an equimolar basis, the only differences are in the speed of action.

The differences in the speed of action of these two agents can be correlated with the rate of disappearance of each agent from the circulation.

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THE INCIDENCE AND SIGNIFICANCE OF SICKLE CELL DISEASE IN DEATHS SUBJECT TO MEDICOLEGAL INVESTIGATION*

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Since Herrick's[15] description of sickle cell anemia in 1910, reports have been appearing with increasing frequency, especially within the last 20 years. Many of these deal with the clinical, pathological, and biophysical aspects of the anemic form of the disease, but many more are concerned with the trait or non-anemic type, usually called sicklemia. It would appear that the old concept of a sharp division between the trait and the anemia is being questioned,[2,12,26,38], and possibly that the former can no longer be ignored as merely a curiosity without clinical significance. Indeed, the term "Sickle Cell Disease" has been suggested by Bauer[1,2] to incorporate the non-anemic types as well as the cases of active anemia which die from their thrombotic complications rather than their anemia *per se*. Since sickle cell anemia is relatively rare compared with the trait[23] (the ratios reported ranging from 1 to 1.4 to 1 to 50, averaging 1 to 40), it seems important to determine the clinical significance of the trait because these people constitute about 10% of the Negro population, and form a large reservoir of potential disease. A review of all the Negro necropsies performed in the Office of the Chief Medical Examiner during the last 2 years was made to determine the incidence of sickle cell disease and its importance in each death, if possible.

Method of Study. All the Negro necropsies from which microscopic material was available were reviewed for 1951-52. Traumatic cases in which death could reasonably have been expected to have been instantaneous or to have occurred within a few minutes were excluded. Those remaining numbered 126, and included all types of death, traumatic, sudden natural, and unattended. From these, 11 cases were found which showed either a full-blown sickle cell crisis with or without other serious disease or merely showed some sickle cells in blood vessels. A brief tabulation of them (Table 1) has been attempted. The following morphological criteria were followed in selecting these cases:

A. CRISES: 1) Characteristic pooling of blood around the splenic follicles. 2) Packing of the liver sinusoids and the glomerular capillaries with massed sickle cells. 3) Distension and plugging of vessels and capillaries in all other tissue sections with massed sickle cells.

B. EVIDENCE OF PAST ACTIVITY: 1) Old vascular thrombi, especially in lungs, spleen, or brain. 2) Hemosiderin deposits in spleen, liver, and bone marrow. 3) Scarred atrophic spleen.

C. EVIDENCE OF TERMINAL SICKLEMIA: Presence of sickle cells in vessels but absence of other above changes.

These findings are well described and agreed upon in the literature[6,7,8,11,13,14,15,19,25,28,29,36]. All histologic material was fixed at necropsy in 10% aqueous neutral formalin.

Case Reports. CASE 1. C. M., a 20-year-old Negro male, was treated by a physician for epigastric and leg pains of one week's duration. No diagnosis was made. He died suddenly at home. At necropsy, there was jaundice, early bronchopneumonia and massive infarction of the spleen, which weighed 340 gm. The heart was of normal size (360 gm.). Because methyl alcoholism was

* Read before the American Academy of Forensic Sciences, February 27, 1953, at Chicago, Illinois.

originally suspected by the medical examiner, a complete toxicologic analysis was run with negative results. Microscopic examination revealed massive agglutination of sickled red cells in distended vessels in all sections. The liver sinusoids were jammed, there was moderate diffuse fatty change, and bile stasis was evident in the canaliculi. The lung showed recent microscopic infarcts and many old organized and partly recanalized thrombi. The spleen was massively infarcted and prominent perifollicular hemorrhages were seen. Iron stains of the spleen, liver and lymph nodes were strongly positive.

CASE 2. E. H., a 3-year-old Negro male, was seen in a clinic 10 days before death, at which time the complaint was "vomiting". No diagnosis was made and he was sent home. One week later he was examined at home by a physician who thought the child had German measles but was not impressed by anything serious. Two days later he became acutely ill, was again seen by the physician, and was taken at once to the hospital, where he expired within a few minutes. No diagnosis was made. Necropsy showed the spleen, liver, and lymph nodes to be enlarged, dark, and firm. Microscopically there was a tremendous sickle cell crisis with typical hepatic and splenic congestion. No other disease was present.

CASE 3. S. R., a 34-year-old Negro male, was in apparent good health until the day before death. There was no past medical history in any way suggestive of sickle cell anemia. The evening before death he complained of epigastric pain, but this was not severe enough to cause him to seek medical aid. He was found dead in bed the following morning. At necropsy, no adequate cause of death could be demonstrated. The spleen appeared normal. Jaundice was not present. A complete toxicological analysis was negative. Microscopic sections showed a severe crisis of sickle cell disease with extreme congestion and packing of the vessels of all organs with sickled erythrocytes, "log-jamming" of the liver sinusoids, and perifollicular splenic hemorrhages. No old or recent thrombi or infarcts were found. The spleen and liver contained moderate amounts of iron pigment. No evidence of other disease was seen.

CASE 4. J. H., a 34-year-old Negro male, died suddenly at his home while sitting on a chair. He had been in poor health for the past 3 or 4 months with a variety of complaints: backache, headache, stomach pains. Despite his illness which was severe enough to keep him from working, he sought no medical attention. Necropsy revealed an emaciated (length 66 inches, estimated weight 110 pounds) Negro male who appeared older than the stated age. There was no jaundice. The spleen weighed 100 gm. On section, small round discrete areas 2 to 3 mm. in diameter, paler and firmer than the surrounding tissue, were seen. The other organs were not remarkable grossly except for a few scattered small round shallow ulcers in the colon. Microscopically there was tremendous vascular congestion of the lung with early thrombi in a few vessels and early areas of pneumonia. No old thrombi or infarcts were seen. All other sections showed intense vascular congestion with packed sickle cells. The colonic ulcers contained no amebae or granulomas, but were composed of a non-specific submucosal inflammation and a few capillary thrombi. The spleen had areas

TABLE 1.—SUMMARY OF PERTINENT FINDINGS IN 11 CASES OF SUDDEN DEATH SHOWING SIMPLE SICKLEMIA OR EVIDENCE OF SICKLE CELL CRISIS AT NECROPSY

			Signs of Previous Activity of Sickle Cell Disease			
Case	*Age*	*Sickle Cell Crisis*	*Infarcts*	*Thrombi*	*Hemosiderin*	*Other Disease*
1	20	+	+	+	+	None
2	3	+	0	0	0	None
3	34	+	0	0	+	None
4	34	+	0	0	+	None
5	55	+	0	0	0	Bronchopneumonia
6	65	+	0	0	0	Lobar Pneumonia
7	8	+	0	0	0	Meningococcemia
8	50	+	0	0	0	Advanced Tuberculosis
9	65	0	0	0	0	Spinal Cord Injury and Pneumonia
10	33	0	0	0	0	Acute Alcoholism
11	34	0	0	0	0	Pulmonary Embolus

of marked congestion and perifollicular hemorrhage as well as foci of early fibrosis. Iron pigment was present in moderate amounts in the bone marrow and liver, and in large amounts in the spleen. The bone marrow also showed a panhyperplasia. No other disease was found and a complete toxicological analysis was negative.

Case 5. T. G., a 55-year-old Negro male, was treated at home for about a week for an upper respiratory infection, but received no antibiotic therapy. He died rather suddenly and unexpectedly. Necropsy was performed at the request of the family. The only significant gross finding was moderate bronchopneumonia. Microscopically, the spleen showed extreme congestion and perifollicular hemorrhage, but no fibrosis. Other organs were intensely congested with masses of packed sickle cells. No old infarcts or thrombi were demonstrable and hemosiderin deposits were absent.

Case 6. S. C., a 65-year-old Negro male, was treated at home for 2 weeks for an undiagnosed illness. The day of his death he was seen by a physician who made a diagnosis of intestinal obstruction and ordered him to the hospital. The patient expired in the emergency room 10 minutes after arrival. Necropsy revealed scleral jaundice, lobar pneumonia, and acute fibrinous pericarditis. Microscopically, there was evidence of a sickle cell crisis in all the organs and the characteristic splenic changes. No old infarcts or thrombi were found and hemosiderin deposits were absent. In addition, an interstitial nephritis and lower nephron nephrosis were present.

Case 7. A. B., an 8-year-old Negro female, had a one day history of headache, malaise, and fever. An examining physician noted nothing specifically wrong and made a diagnosis of "grippe". He did state to the family that there were no signs of meningitis. The child received only aspirin for treatment. She was found dead in bed the following morning. At necropsy, a few very faint spots were seen on the trunk and several observers were undecided as to whether or not these were actually petechiae. No lesions were seen elsewhere. There was minimal active primary complex pulmonary tuberculosis, slight congestion of the left adrenal, and aspiration of a small amount of gastric contents. The brain was normal. A postmortem heart blood culture yielded a growth of *Neisseria meningitidis*. Microscopically, the brain showed no meningitis and the adrenals were without hemorrhage or focal degenerations. A piece of skin from the questionable petechia showed nothing. There was typical evidence of a sickle cell crisis seen in all organs. Hemosiderosis or thrombosis were absent.

Case 8. J. E., a 50-year-old Negro male, complained of weakness and loss of appetite for the past several days. His sister stated that he appeared quite ill, staying in bed most of the time, and had a persistent dry cough. That evening he was found in his room on the floor, gasping for breath. He expired before medical aid could be obtained. Necropsy revealed a moderately emaciated man with no evidence of jaundice. There was apical fibro-caseous pulmonary tuberculosis with miliary involvement of both lungs, spleen, liver, and adrenals. The spleen weighed 200 gm. An adhesive pericarditis was present. There was extensive genito-urinary tuberculosis with bilateral pyonephrosis, ureteritis, cystitis, epididymitis, and orchitis. Acid-fast stains revealed countless bacteria resembling Mycobacterium tuberculosis. In addition, a full blown histologic sickle cell crisis was present. Splenic fibrosis, old thrombi, or hemosiderosis were not seen.

Case 9. W. M., a 65-year-old Negro male, suffered a spinal cord injury with paralysis. Three months later he developed pneumonia and died. Necropsy showed an old fracture dislocation at D7-D8 with myelomalacia and confluent bronchopneumonia. Only a few scattered sickle cells were seen microscopically.

Case 10. G. R., a 33-year-old Negro female, was last seen alive at 11 P.M. following a heavy drinking bout. She was found dead in a chair the next morning. Necropsy revealed no anatomical cause of death. A blood alcohol determination showed 0.38%, a finding compatible with death by acute alcoholism. Microscopic examination gave no additional information. A few congested vessels with some sickle cells were seen. The spleen was normal except for one low power field in which there was a solitary but very distinct perifollicular ring of hemorrhage.

Case 11. F. A., a 34-year-old Negro female, complained of chest pain for one week and was treated for pleurisy. She died suddenly at home. Detailed information about her death was unavailable. Necropsy revealed a large saddle pulmonary embolus. The uterus was enlarged (2100 gm.) and studded with multiple leiomyomas. An early pregnancy was also found. No source of the embolus could be demonstrated; however, the leg veins were not dissected. Microscopic examination revealed nothing except some scattered sickle cells. The spleen was normal.

Discussion. From the tabulation in Table 1 it is apparent that these cases fall fairly well into 3 groups: sickle cell crisis alone, sickle cell crisis with other disease, and terminal sicklemia without crisis in the presence of other disease. Therefore, the cases will be discussed in groups rather than individually.

CASES 1 TO 4. These 4 cases are believed to represent the "active" disease or sickle cell anemia. Since none of them received any diagnostic study before death, the presence or absence of anemia cannot be proved. However, it is of interest to note that 2 reached the ages of 24 and 34 without previous illness of sufficient severity to warrant medical study. One of these died very unexpectedly within 12 hours after the onset of epigastric pain, the other died suddenly within one week after similar complaints. The latter was seen during this time by a physician who apparently was not impressed by any serious disease. The child presented an identical picture, that is, relatively minor complaints and apparent good health until a rapidly progressive and fatal deterioration supervened. The fourth case was obviously ill for some time and can be considered as more or less typical sickle cell anemia. However, he had not sought medical attention despite his severe illness. The possibility of sickle cell anemia was not considered in any of these cases which were attended before death. The pathologic findings of massive vascular congestion by packed sickle cells and perifollicular splenic hemorrhages are characteristic of sickle cell crisis[8,27]. The findings of old thrombi in Case 1 and hemosiderosis in all but Case 2 suggest active episodes in the past[8,33], which may have been mild enough to obviate medical attention or escape notice by a physician. If splenic fibrosis can be used as a criterion for the degree of activity[33], Case 4 corresponds with this concept both clinically and pathologically. The child showed neither thrombi nor hemosiderosis and it may well be that this episode constituted his original crisis. It is of interest to note that crises have been reported in young infants[3], the earliest being one month of age[5]. In none of these cases was other serious disease present.

In summary, 3 cases or 2% of this series represent sickle cell anemia in a mildly active and undetected form in which death was due to this entity alone and was either sudden or unexpected.

CASES 5 TO 8. In all these cases, the histologic picture of an acute crisis was just as striking as in the first group. Without exception, however, evidence of previous activity was absent, that is, hemosiderosis, old thrombi, kidney scars, splenic infarction or fibrosis were all absent. Three of these patients were over 50 years of age, considerably beyond the usual life expectancy of people with active sickle cell anemia[43]. Of the serious other disease present, pneumonia was observed twice and meningococcemia once, both of which conditions are well known to produce anoxemia and shock, respectively. These factors will be discussed later. Two cases also had tuberculosis (7 and 8), in one of which (8) it was the fatal disease. The higher incidence of tuberculosis in sickle cell anemia has often been mentioned, and a recent study[39] again bears this out. However, it also appears that the trait itself has an unfavorable reaction, the trait being twice as common in Negroes with tuberculosis as in the general hospital Negro population[38]. The role played by the crises in these cases is difficult to evaluate with the exception of Case 5. Here, the amount of disease which was present is not usually the cause of death in itself, a previous serious illness or injury generally being the primary factor. It does not seem un-

reasonable to assume that the sickle cell trait, under the duress of anoxemia, provided this factor in the form of an acute crisis with a resulting mechanical vascular blockade of all tissues and death. In Case 7, the absence of petechiae and degenerative or hemorrhagic adrenal lesions suggests the possibility of death from a sickle cell crisis initiated by shock before the full effects of the bacterial toxins could be exerted. In Cases 6 and 8, the major pathology was so far advanced that the sickle cell crisis can be considered of no consequence in the outcome.

CASES 9 TO 11. These cases were included to represent terminal sickling, and indeed some of the sickle cells may have formed after death. In Case 11, because of the absence of morphologic changes suggesting active sickle cell disease, it was felt that the pulmonary embolus was most likely related to the large and deformed uterus. It is interesting to note that in Case 10, a solitary splenic lesion had formed and possibly had she survived a few hours longer, a full blown crisis may have developed. This would suggest that the basic difference between this group and the previous group is not one of kind but of degree. The addition of this group of cases brings the overall sickling rate to 8.7% in this series, a figure which agrees with the national average[29].

Comment. The clinical manifestations of classical sickle cell anemia are well known and need no repetition. However, the literature is rapidly amassing an amazing variety of clinical symptoms and pathologic changes. Cerebral complications have been widely discussed, including hemiplegia and cranial nerve palsies[19,32], multiple focal necroses and hemorrhages[4,34,40], massive cerebral infarction[6], sinus thrombosis[17], and electroencephalographic abnormalities[16]. In one of these reports, anemia was absent[31]. Cardiac changes include cor pulmonale[42] and simulated coronary occlusion, the latter both clinically and electrocardiographically[18,44]. Focal myocardial degenerations[41] and an increased P-R interval on the electrocardiogram[21] are described. The latter in conjunction with cardiac enlargement which is often present by Roentgen-ray may lead to a diagnosis of rheumatic myocarditis. Although these 2 diseases do not appear to be especially common together[21], well documented cases of such a coexistence are reported[25]. Focal bone marrow infarctions with disseminated fat emboli have been observed[37]. In other cases, fat emboli without marrow infarction have appeared, and the possibility of these arising from lipoid released from the destroyed red cell membranes has been entertained[10].

After reading these reports it soon becomes apparent that "comparatively few Negroes come to necropsy in whom the diverse manifestations of the disease do not have to be considered[26]." Of particular interest to us have been the reports of sudden or unexpected death[10].

Despite much investigation, the final chapter in sickle cell disease is far from being written. The finding of different electrophoretic patterns of hemoglobin in the anemic and trait conditions[24,29] does not alter the fact that sickling occurs in both cell types, if the stimulus is great enough[24]. Oxygen tension and pH are important factors in the degree of sickling[22]; furthermore, *in vitro* studies have shown also a direct relation between sickling and the leukocyte level, temperature, and extent of bacterial contamination[28]. Sherman observed that when susceptible cells were subjected to high concentrations of nitrogen, 2 types of deformity could be produced, a typical sickle shape if done slowly, or a granular or holly-wreath form if

done rapidly. Since the difference in behavior between trait and anemia cells appears to be one of degree rather than kind[1,24], it should be expected that under a severe enough stimulation from other disease, a sicklemia patient may develop a crisis without any previous anemia. Indeed, such instances are being more frequently reported[1,2,12,26,34].

The mechanisms concerned in the development of the crises are even more obscure. Three theories have been proposed[30]: 1) A hyperhemolytic process. 2) Bone marrow aplasia. 3) A combination. The so-called aplastic crises are interesting, and in view of the shortened survival time of anemia cells as compared with the normal survival time of trait cells[29,30,31], it is quite possible that anything producing a temporary decrease in the bone marrow output could readily result in a rapidly developing anemia, anoxemia, and subsequent sickling crisis. Other mechanisms are necessary, however, to explain the crises in trait patients. The theory proposed by Tomlinson[35] and further developed by Kimmelstiel[20] supposes that the crisis, set off by any factors which produce a decreased oxygen tension in the blood, induces a state of shock which furthers the anoxemia and produces vasospasm. This leads to tissue anoxia, capillary stasis, and consequently more sickling, that is, a vicious circle is established. Of Tomlinson's 7 cases seen before death, 5 were in shock. This theory offers several avenues by which a crisis may be initiated and is applicable to both the anemic and the trait conditions, the former being capable of spontaneous onset, the latter needing a trigger mechanism in the form of a shocking or anoxic lesion. It is of interest to note that 3 of our 4 cases of crisis imposed upon other disease had as the primary disease pneumonia (anoxia) or meningococcemia (shock).

Summary and Conclusions. 1. Of 126 selected Negro necropsies, sudden or unexpected death from sub-clinical sickle cell anemia without other disease occurred in 3 cases or 1.4%.

2. In 4 cases, or 3.1%, a terminal crisis developed in the course of other severe disease. For reasons previously mentioned, it is felt that these represent inactive sicklemia stimulated into active disease. In 2 of these 4 cases the sickling crisis may well have been the deciding factor in the fatal outcome.

3. In 6 cases, or 4.7% sickle cell disease was thought to be either the sole cause of death or an important contributing condition.

4. Patients with sicklemia should be regarded as increased risks during shocking or anoxic types of disease or injury. It is possible that as yet undiscovered individual differences in the sicklemic group may be basically responsible for the development of crises in some and the absence in others under the same stress.

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A COMPARISON OF THE EFFECTS OF TERRAMYCIN HYDROCHLORIDE AND AMPHOTERIC TERRAMYCIN ON THE FECAL FLORA OF HUMANS*

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Antibiotic prophylaxis prior to intestinal surgery has been advocated by a number of clinicians and investigators. The consensus of this group is that the action of broad spectrum antibiotics and chemotherapeutic agents serve to "sterilize" the large intestine and thus decrease the possibility of generalized peritonitis after radical operations. One of the antibiotics for this purpose is Terramycin (brand of oxytetracycline). To date, all the investigations of the action of this agent on the fecal flora have been performed with the hydrochloride form. Recently, an amphoteric form of Terramycin base has been released for distribution. It was hoped that Terramycin in this form, when taken orally, would cause less gastric disturbances than does the hydrochloride. The clinical results have supported this contention[15]. A survey of the literature revealed a lack of bacteriological data concerning the action of amphoteric Terramycin on the fecal flora. It was the purpose of this investigation to determine the relative action of Terramycin in both its amphoteric and hydrochloride forms.

Finlay *et al.*[6] demonstrated that the organisms normally present in the intestinal tract, when tested *in vitro*, showed a species variation in the susceptibility to the action of Terramycin hydrochloride. Most strains of *Aerobacter aerogenes* were inhibited by concentrations as low as 1 mcg./cc., and the majority of strains of *Escherichia coli* were completely inhibited by concentrations of 5 mcg./cc. Many strains of *Proteus* required a Terramycin hydrochloride concentration of greater than 1000 mcg./cc. before inhibition was complete.

Substantiating the findings of Finlay *et al.* were those of Bliss, Warth, Chandler and Long[2]. They showed that strains of *E. coli* and *A. aerogenes* were inhibited by concentrations of Terramycin hydrochloride ranging from 0.6 to 2.5 mcg./cc. Streptococci and staphylococci showed susceptibilities in concentrations ranging from 0.04 to 0.31 mcg./cc. and 0.16 to 0.31 mcg./cc. respectively. All strains of *Proteus* appeared to be partially resistant to the action of this agent, and minimal inhibitory concentrations were found to

* Terramycin was supplied through the courtesy of Charles Pfizer & Co., Inc.

be between 10 mcg./cc. and more than 100 mcg./cc.

Feeding experiments involving rats fed various diets supplemented with Terramycin hydrochloride showed significant reductions in total count, both aerobic and anaerobic: however, an increase in fecal streptococci was noted, regardless of the type of ration[11,15].

The recent reports by Baker and Pulaski[1] indicated that the normal intestinal flora of 11 patients receiving Terramycin hydrochloride was rapidly altered. An increase in *Proteus* species was demonstrated concomitantly with the decrease of the coli-aerogenes group. There was little change in the number of enterococci. Dearing and Heilman[3,4] reported similar findings with the antibiotic Aureomycin. Linsell and Fletcher[9] noted that the disappearance of the coli-aerogenes group caused by Terramycin hydrochloride prophylaxis was accompanied by an abrupt decrease in the number of enterococci. Similar results were reported by Herrel, Heilm and Wellman[7].

Materials and Methods. Three 250-mg. capsules of Terramycin hydrochloride were administered orally every 6 hours for 5 days to a group of 7 individuals essentially free from gastrointestinal disorders. The same schedule of dosage of amphoteric tablets was given to a second group of 13 individuals.

The feces of each patient were examined on 2 days prior to administration of the antibiotic and daily thereafter for the entire period of treatment and one day after cessation of treatment. Common bacteriological plating techniques were employed. Enumeration of the total viable aerobes was made on Tryptone glucose extract agar, and MacConkey agar was used for the detection of coliform bacteria. On both of these media a thin "sandwich" layer of medium was poured to inhibit the spread of *Proteus* colonies. Azide dextrose agar was used for the estimation of enterococci. The above plates were incubated at 37° C. for 48 hours. Urea ricinoleate agar[16] was used for the enumeration of *Proteus* species. These plates were incubated at 37° C. and counted at 24 and 48 hours.

To determine whether or not there was a correlation between the amount of amphoteric or hydrochloride Terramycin ingested and the predominant species of enterococci present, colonies were picked at random from the Azide dextrose agar plates and classified as to species.

Results. The arithmetic mean of viable plate counts obtained on 7 patients receiving Terramycin hydrochloride and 13 receiving amphoteric Terramycin is depicted in Figs. 1, 2, and 3.

The composite curves do not differ appreciably from those obtained on individual patients.

COLIFORMS. As demonstrated in Fig. 1, the action of both the amphoteric Terramycin and Terramycin hydrochloride on the coliform group was, for all practical purposes, identical. It is shown that these organisms number between 10^6 and 10^7 two days before administration of the antibiotic. After 72 hours of treatment the coliforms were virtually eliminated.

In a few cases, resistant coliform organisms developed during the course of therapy, but this was the exception rather than the rule.

PROTEUS. The examination for *Proteus* species was positive in about 50% of the specimens obtained from patients receiving Terramycin in the amphoteric form. Much difficulty was encountered with urea ricinoleate agar in the enumeration of *Proteus;* consequently, these results are not included in the data. However, the trend of the count in these cases indicated a much slower rise in numbers, than that reported by Baker and Pulaski[1] using Terramycin hydrochloride. This view may be further substantiated by the slower rise in total count in patients receiving amphoteric Terramycin.

ENTEROCOCCI. The effect of treatment with Terramycin hydrochloride was such that the enterococci counts increased a hundred fold. The maximum increase was evident approximately 72

hours after the start of treatment (Fig. 2).

The stools of patients receiving amphoteric Terramycin showed only a slight increase in the numbers of enterococci present during this same time interval.

It was found that there was no correlation between the species of enterococci present and the amount of Terramycin ingested either in the amphoteric or the hydrochloride form.

TOTAL AEROBIC COUNT. As demonstrated in Fig. 3, the total aerobic count on patients receiving Terramycin hydrochloride rose gradually until it reached a maximum at approximately 72 hours. At this point there was a thousandfold increase in numbers of microörganisms as compared to the Terramycin hydrochloride-free stool.

With the amphoteric Terramycin, a slower rise in total aerobic count was found. At the corresponding time interval of 72 hours, there was only a tenfold increase over the original count.

REACTIONS OF PATIENTS. The most frequent side effect with Terramycin

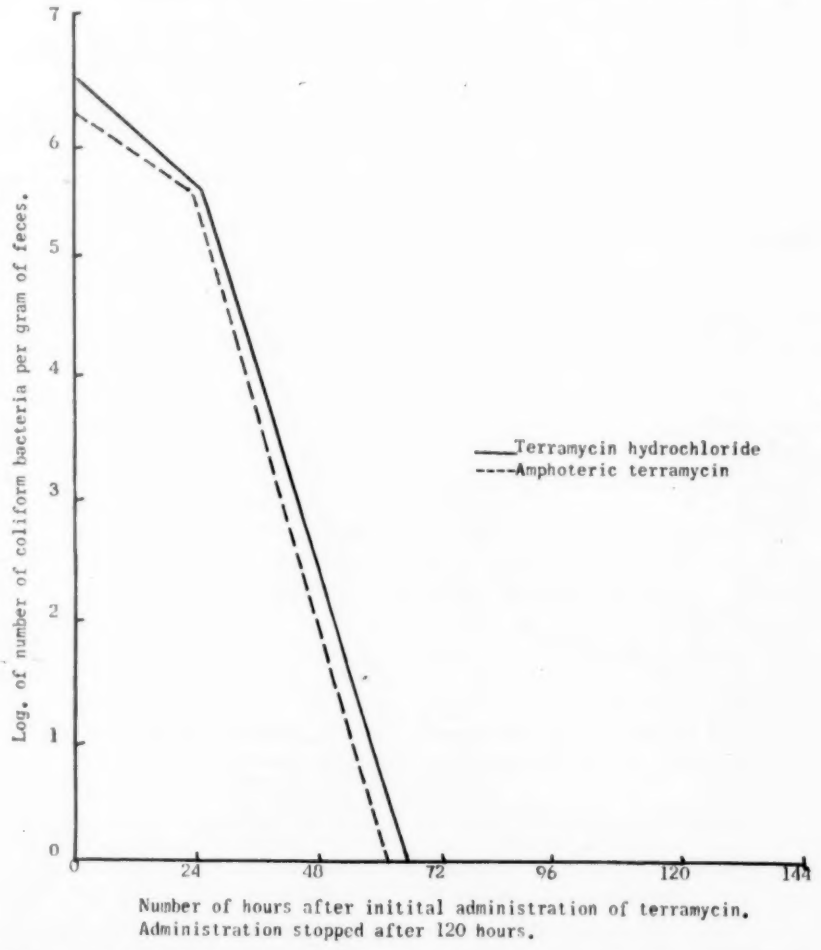

Fig. 1.—The Action of Terramycin on the Numbers of Coliform Organisms in the Feces.

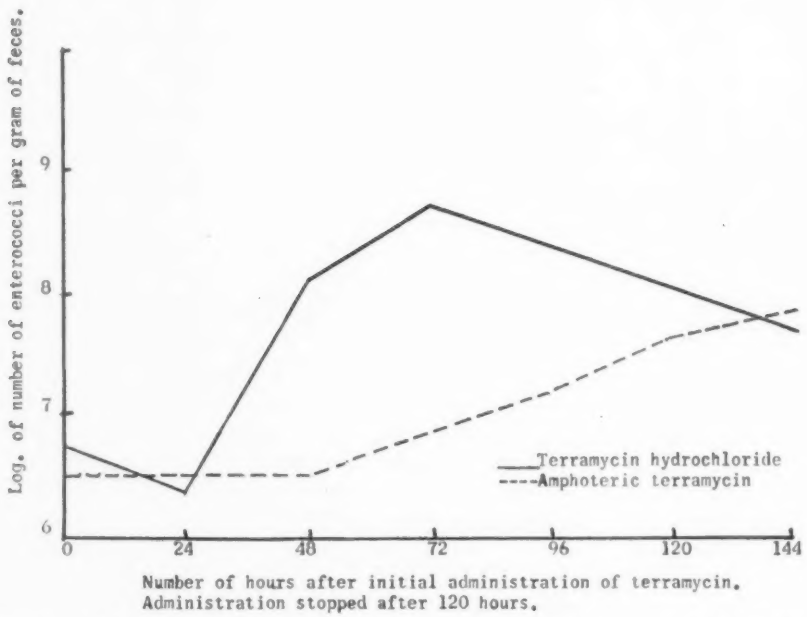

Fig. 2. – The Action of Terramycin on the Numbers of Enterococci in the Feces.

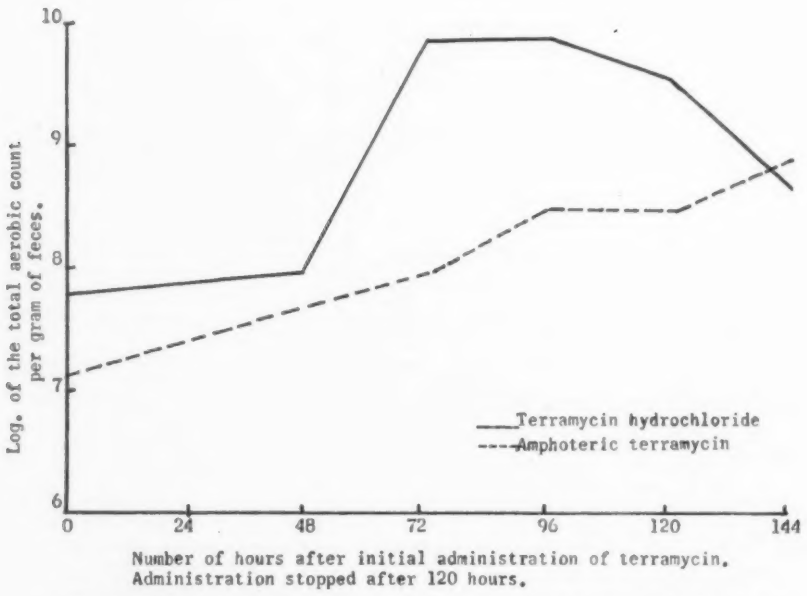

Fig. 3.–The Action of Terramycin on the Total Aerobic Count of Feces.

hydrochloride was a gastrointestinal disturbance evidenced by a severe diarrhea. In 43% of the patients receiving Terramycin hydrochloride, the dosage was stopped after the third day of treatment because of the violent reaction. Two extreme cases required immediate medical attention. These same types of reactions have been reported by other investigators[5,8,12].

A perianal irritation was noted in virtually all cases using either the amphoteric or the hydrochloride form[10].

Discussion. Individuals utilizing chemotherapeutic "sterilization" of the bowel prior to surgery have assumed that the disappearance of the coliform organisms from the feces denotes the absence of all the pathogenic organisms from this area. In so doing they have taken too lightly the possibility of an increase in numbers of other fecal organisms. Spaulding *et al.*[13] state that "orally administered Terramycin (hydrochloride) is not an effective intestinal antiseptic. The principal effect is to increase the total number of microorganisms and to cause multiplication of *Proteus* and enterococci, which, if they escape from the bowel, may be more prone to cause infection than the original flora."

Any chemotherapeutic agent that serves to inhibit only one of the groups of organisms present in the gastrointestinal tract will disturb the balance of the normally present microflora.

Terramycin hydrochloride and the amphoteric form of Terramycin primarily exhibit inhibitory action against the coliform bacteria. There is virtually no observed difference on the rate of disappearance of this group of organisms when either of the agents are used.

However, during the course of disappearance of the coliforms when Terramycin hydrochloride is used, the balance of organisms is so disturbed that the numbers of *Proteus* and enterococci, as well as the total count, is increased 1000 to 10,000 times at 72 hours[13].

It would seem that the action of the amphoteric form does not disturb this balance to so great an extent, since the numbers of *Proteus* and enterococci as well as the total count are increased only 10 to 100 times at 72 hours.

This increase might be explained in part by the fact that *E. coli* is capable of producing a complex mixture of antibiotics, which have been designated colicines[14]. These are believed to be primarily bacteriostatic against pathogenic Enterobacteriaceae, but they have been shown to be inactivated by proteolytic enzymes; consequently, their action in the intestine is assumed to be negligible. The possibility remains, however, that related substances not yet isolated and not inactivated by proteolytic enzymes may function as an inhibitory agent against the *Proteus* group.

If these inhibitory agents such as colicines and others remain in the intestine in the absence of their progenitor, *E. coli*, Terramycin hydrochloride must exhibit antagonistic action against these agents and thus allow the numbers of *Proteus* to increase without restraint. Since, in the presence of amphoteric Terramycin the numbers of coliforms still disappear, but the numbers of *Proteus* do not rise at such a rapid rate, it may be inferred that the amphoteric form is either not antagonistic to colicines that inhibit *Proteus* or is antagonistic to *Proteus* itself. This supposition would tend to support any contention of a difference in antibacterial action of both forms of the antibiotic.

Clinical evidence indicates a possible difference in pharmacological action of these two forms of Terramycin, since side effects using the amphoteric form were less drastic than those encountered in the hydrochloride forms.

If the surgeon believes that the bowel should be free of coliform organisms prior to an intestinal operation, it is strongly suggested that amphoteric Terramycin be used rather than the hydrochloride because: (1) Coliform bacteria are removed just as rapidly with the amphoteric as with the hydrochloride. (2) Seventy-two hours after the start of therapy with the amphoteric form, the enterococci remain at a normal level in contrast to the hundredfold increase obtained with the hydrochloide. (3) Although only 50% of the specimens tested showed *Proteus* species with the amphoteric, they did not show a dramatic rise in 72 hours as is so characteristic of hydrochloride prophylaxis. (4) Total count per gram of feces increases approximately tenfold after 3 days of treatment with the amphoteric Terramycin, whereas with the hydrochloride the increase in total count is 100 to 1000-fold. (5) Gastrointestinal disturbances as well as other toxic reactions are far less severe with the amphoteric than with the hydrochloride.

Summary. 1. Twenty patients were put on a regimen of 3 gm. of Terramycin daily, administered 750 mg. orally every 6 hours. Seven of these patients received the hydrochloride form; 13 received the amphoteric. Stools were examined daily.

2. The coliform bacteria disappeared after 72 hours of treatment with both forms of the antibiotic.

3. Patients receiving amphoteric Terramycin exhibited a lower number of enterococci and total aerobes per gram of feces than those patients receiving the hydrochloride.

4. Gastric disturbances were less frequent with the amphoteric form of Terramycin.

5. A difference in the mode of action of these two forms of the antibiotic is suggested.

We wish to thank Dr. Howard P. Kennedy, Assistant Visiting Physician to The Springfield Hospital, and Dr. William Kaufmann, Pathologist-in-Chief of The Sprinfield Hospital, for their supervision of the patients undergoing treatment and for their many valuable suggestions.

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THE TREPONEMAL IMMOBILIZATION TEST

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IN view of the well demonstrated non-specificity of the reactions of the serologic tests used in the diagnosis of syphilis, considerable effort has been directed to the development of a procedure which would with certainty indicate the presence or absence of this disease. In addition, the nature of the antibody detected in syphilitic serums by the non-specific antigens employed in the conventional serologic procedures is unknown except for the fact that it is similar to other antibodies in molecular weight and associated chiefly with the gamma globulin fractions of serum. Accordingly, when, in 1949, Nelson and Mayer[55] adapted the long known principle[73] that the serum of syphilitic animals or man contained an antibody that combined directly with virulent *Treponema pallidum*, to the definitive diagnosis of syphilis, we[6] hailed this test (Treponemal Immobilization Test: T.P.I.) as the outstanding contribution to syphilology in 1949 if not in recent years. Since then there has been adequate evidence to warrant this enthusiastic acclaim.

Nelson and Mayer mixed an emulsion of motile treponemes (in a medium Nelson[52] had previously devised for maintaining the organisms alive and motile for from 5 to 10 days) with syphilitic or normal serum plus complement, and observed the result directly under the microscope. While nothing happened in normal serum within 15 to 18 hours under these cir-

cumstances, syphilitic serums immobilized and killed the organisms. The possibilities of this procedure captivated the attention and imagination of a vast number of investigators the world over and it has provided useful tools to study many of the unsolved problems in syphilis diagnosis and immunity.

The search for antibodies in syphilitic serum preceding the development of Nelson and Mayer's *Treponema pallidum* immobilization procedure had yielded rather confusing results. In 1944, Stokes, Beerman and Ingraham[67] summarized the earlier efforts as follows:

"The extensive literature on this subject may be followed in the summaries of Mulzer (Jadassohn Handbuch) and Colonel Harrison (1931); Kolmer, Kast and Lynch (1941) and Kolmer (1942) bring the literature of the subject up-to-date. While it has been shown that agglutinins and lysins for *Spirochaeta pallida* are formed, they are insignificant as far as inhibitive effect on the disease is concerned. Eberson's claim for virulence reducing properties in the blood serum of latency in man and Jauregui and Lancelloti, who claimed curative properties for llama serum have failed of confirmation. The most interesting current discussion concerns the relation between the recognized agglutinins for *Spirochaeta pallida* and the Wassermann reagin. Kolmer and his group believe they have shown them to be fundamentally different, and Beck (1939) likewise, while Eagle and Hogan (1940) believe the two substances to be identical, and to be in fact, true spirochetal antibodies. Turner (1939) showed experimentally that in the course of syphilitic infection specific humoral antibodies develop which can be demonstrated by an appropriate "protection test". Tani (1940) concluded that emulsions of *Spirochaeta pallida* in tissue produce no antibodies or immune reaction demonstrable with syphilis serum *in vitro*."

Turner, Kluth, McCleod and Winsor in a later study[75] again employing protection tests, used serums from human beings in place of rabbit serum previously reported in 1939 by Turner. With this technique, serums from patients with secondary, latent or so-called tertiary syphilis exerted a definite inhibitory effect on the development of syphilitic lesions in rabbits as compared with serums from non-syphilitic patients. Serums from patients with primary syphilis in general behaved more like the serums from non-syphilitic persons. They concluded that persons with secondary, latent and tertiary syphilis as a group possess humoral antibodies which kill or at least inhibit the multiplication of *Treponema pallidum*, and that these protective antibodies, probably play a significant role in acquired immunity to the disease.

Recent studies by a group of other investigators confirmed the presence of multiple antibodies in syphilitic serum. D'Alessandro[12] working with palligen demonstrated the presence of three distinct antibodies in syphilitic serum: antilipidal, antitreponemal (thermolabile) and antitreponemal (thermostable). He expressed the belief that in early primary syphilis the antitreponemal antibodies manifest themselves before the antilipidal antibodies. In secondary and tertiary syphilis both types run a parallel course. In cases of prenatal syphilis the antilipidal antibody often exists alone. The work of D'Alessandro was confirmed by Puccinelli and Oddo[61] who described the technique of demonstrating the three antibodies[59,60]. It is too early to make any clear statement about the relation of the antibody responsible for the adhesion-disappearance phenomenon and

the treponemal immobilization antibody[49].

Nelson-Mayer Treponema Pallidum Immobilization Test (T.P.I.) TECHNIQUE: In their contribution, Nelson and Mayer[35] have experimentally demonstrated a heretofore undetected antibody in the serum of syphilitic animals and human beings. This antibody has been designated as an immobilizing antibody, and, as the name indicates, it has the ability to immobilize virulent *T. pallidum* organisms. The present serologic tests for syphilis are carried out with lipid antigens of mammalian tissues and serve to detect syphilitic infection with a high but not entirely satisfactory degree of specificity. In addition, these tests do not serve as an index of immunity. This is especially the case in latent syphilis, when the titer of reagin decreases while the disease progresses. Nelson and Mayer believed that the immobilizing antibody was related to the immunologic processes. In their experiments they attempted (1) to demonstrate the immobilizing activity due to a specific antibody in the presence of complement and to show that immobilized spirochetes are non-infectious or dead; (2) to study factors that affect the measurement of the immobilizing antibody in the serums of syphilitic persons; (3) to demonstrate the presence of antibody in serums from animals and human beings in various stages of syphilitic infection, and (4) to differentiate the immobilizing antibody from reagin.

The extraction and maintenance of virulent *T. pallidum* from rabbit syphilomas was described by Nelson in 1948[52]. When spirochetes are suspended in Nelson's complex fluid medium, they are extremely active. There are no intermediate phases of motility resulting from the action of antibody and complement, that is, sluggishly motile forms. The organisms are either fully active or completely nonmotile. In the tests described, the immobilized spirochetes are not lysed nor do they agglutinate. Accurate determination of the total organisms present and percentage of motility can be made because repeated counting of the same motile treponeme in adjacent fields is unlikely in view of lack of translational movements of the spirochete. The complement used in the immobilization antibody tests is obtained from the guinea pig. In their study Nelson and Mayer used 5 groups of serums for testing the immobilizing antibody activity: 1) nonsyphilitic rabbits; 2) untreated syphilitic rabbits inoculated with Nichols strain with infection from 3 to 9 months; 3) serums of patients with primary and with secondary syphilis confirmed by dark field examination; 4) serums from nonsyphilitic persons and 5) serums from patients with disease other than syphilis. All procedures in this test are carried out under strict aseptic precautions. All steps involving the exposure of the organism to adverse living conditions are carried out as quickly as possible to obtain optimal survival of the organism. The test procedure itself involves pipetting 1.7 cc. of filtered treponeme suspension (10^7 organisms per cc.) into a test tube of appropriate size and adding 0.2 cc. of serum to be tested and 0.1 cc. of guinea pig complement. Control tubes containing 1.7 cc. of treponeme suspension, 0.1 cc. of complement and 0.2 cc. of ultrafiltrate of serum are tested simultaneously. The tubes are incubated at 35° C. in Brewer anaerobic jars with 5% carbon dioxide and 95% nitrogen. The percentage of motile organisms is determined by examining 50 successive treponemes as previously described. Counts were made at the start of the test and at 4, 8 and 16 hours. In the survey experiments, counts were taken at 16 hours, as this was the time showing

optimal results. At the termination of each test failing to produce immobilization, the contents were tested for the presence of active complements in order to eliminate the possibility of false negative results.

Serums of healthy and of syphilitic rabbits had no immobilizing influence on *T. pallidum* in the absence of guinea pig complement. However, in the presence of complement there was a marked reduction in motility of the organism in the syphilitic serum pool but not in the normal serum. In normal serum with complement, there was 96% motility at 12 hours, and 84 to 92% motility at 24 hours in dilutions of 1:10 and 1:1,000 respectively. Syphilitic serum diluted with complement to a fluid dilution of 1:10 gave a 2% motility at 12 and 24 hours, while in a dilution of 1:1,000 there was motility at 92 and 84% at 12 and 24 hours respectively. In control tubes there was 92% motility for the same period. Since complement is necessary for immobilizing effect, this would suggest that immobilization is an antibody against *T. pallidum*.

Some previous tests showed that inactivated normal serum in concentration of 40% produced a significant inhibition on survival of spirochetes in the absence of complement and some immobilization occurred in 20% solution. However, in concentration of 1:10, there were no immobilizing properties; thus this percentage and a minimum of 16 hours' incubation was used in survey experiments. Therefore, in survey experiments all serums were employed in dilutions of 10%, and mixtures were incubated at 35° C. for 16 hours.

Certain factors influence the outcome of the tests. The rate of antibody action increased with temperature; as a result, the sensitivity of antibody action at any given time interval also became greater. The immobilizing activity of fresh guinea pig serum is attributed to the complement content. Immobilizing activity was manifest only in the presence of complement and was maximal when the final dilution of guinea pig serum was 1:10 to 1:20.

In order to demonstrate that the effect of the antibody was treponemicidal, Nelson and Mayer[55] found it necessary to prove the nonmotile organisms were dead. Total counts of percentage of motile organisms in mixtures of treponemes, serum and complement were determined after incubation for 16 hours at 30° C. Motility readings of complement with ultra-filtrate serum control was 80%; of complement plus normal serum, 78%, and of complement plus syphilitic serum 4%. Then 0.1 cc. portions of the suspensions were inoculated intracutaneously into the backs at 4 sites on each of 2 rabbits. This permitted the comparison of 3 samples in a single animal, eliminating the variation of individual response. Significant differences in the incubation period and the size of the resultant lesions were noted between the suspension of 4% of motile organisms and the specimens containing 78 to 80% of motile organisms. It was concluded that a significant proportion of the spirochetes in the mixture of syphilitic serum plus complement were rendered noninfectious or presumably dead, though the data do not give a quantitative estimate of the spirochetes so affected. It is also probable that the immobilizing antibody rendered the organisms more susceptible to the host's defense mechanism.

Using another batch of *T. pallidum*, a control tube of ultra-filtrate serum and complement with a 90% motility after 16 hours at 35° C. and a tube of syphilitic serum and complement with a 4% motility rate, the authors did similar intracutaneous experiments. Lesions positive for treponemes on dark field examination developed in 6 days at the sites inoculated with the control

suspension (90% motile), whereas at only one site a similar lesion developed on the 28th day following the inoculation of the syphilitic serum-complement suspension (4% motility). It was estimated that less than 500 viable treponemes were present in a total of 500,000 (0.1%) which would be compatible with 1% motility in a count of 50 treponemes. This further indicated that immobilization by antibody and complement renders treponemes noninfectious or nonviable.

A series of 20 normal rabbit serums and 20 serums from untreated syphilitic rabbits were tested for immobilizing antibody and for reagin titer. Motility was determined at 35° C. after 16 hours. The controls showed 90% motility; normal rabbit serums with complement had a motility range from 70 to 90%, whereas syphilitic rabbit serums with complement had a motility range of 0 to 12%. All 20 serums of syphilitic rabbits showed a marked degree of mobilizing activity. In the latter group, there was no immobilization in the absence of complement.

Serums from 20 nonsyphilitic persons and from 20 patients with confirmed primary or secondary syphilis were tested, regardless of the serologic titer. In addition, serums were obtained from 20 patients suffering from diseases other than syphilis. Of the 20 patients with primary syphilis, 7 had serums negative for immobilizing antibody, 10 had serums positive for such antibody, and 3 had serums showing a slight degree of immobilization. All serums from patients with secondary syphilis showed a marked degree of immobilizing activity. Serums of nonsyphilitic persons showed no immobilizing activity. Of patients with disease other than syphilis, serums from 16 showed no immobilizing action, whereas serums from 4 did have immobilizing effect. These 4 patients had been receiving penicillin, and it is quite possible that they had sufficient of the antibiotic in the serum to inactivate the spirochetes. It is therefore advisable to obtain serums before antibiotics, such as bacitracin, penicillin and aureomycin, are administered.

In order to study the relation of reagin to immobilizing antibodies, absorption experiments were conducted. By means of two absorptions with use of Eagle antigen, lipid particles were removed from serologically positive serums by centrifugation and filtration, removing titrable reagin. In these serums, subsequently tested for immobilizing antibody, there was no decrease in the immobilizing activity after removal of reagin. Repeated tests showed the same clear-cut results, definitely indicating that immobilizing and reagin activities are due to separate antibodies.

Finally, it was demonstrated that reagin titer drops as the temperature increases, but there is no corresponding decrease in immobilizing activity. Whereas reagin titer drops progressively when syphilitic serum is exposed to temperatures of 56°, 60°, 64° and 68° C. respectively, the immobilizing antibody withstands temperatures as high as 70° and 72° C. The latter thermostability is unusual for antibodies, but such thermostability is noted in the flagellar component of hog cholera bacillus. An *in vitro* technique for the detection and measurement of specific antibody produced during a syphilitic infection of the immobilization antibody activity offers an approach to certain fundamental problems on syphilis infection: 1) the incidence and titer of the immobilizing antibody in various stages of syphilitic infection; 2) the rate of appearance of the antibody following infection, and its quantitative relationship to the development of immunity as measured by resistance to infection; 3) the possible absence of immobilizing antibody in

nonsyphilitic persons whose serums contain reagin or in the biologic false-positive reactors; 4) the immunologic relationship in experimentally induced yaws and other spirochetoses; 5) the possible immunologic variations among different strains of *T. pallidum*. It was felt that it was necessary to simplify and investigate thoroughly the technical aspects of the immobilizing antibody test before it can have practical applications. In this early study, Nelson and Mayer felt that the chief value of their test would be in the detection of the biologic false-positive reactors (see below).

Nelson and Mayer's report soon fired the imagination of workers scattered over the world and it has been followed by a flood of publications dealing with its application on the T.P.I. test to clinical diagnosis; the differentiation of true from falsely positive serologic reactions; the problems of immunity in syphilis; the inter-relationship of various spirochetes; and the mechanism involved in the process of immobilization. In the present compilation, as critical as one can be in a field so recent, the available information on the above topics will be discussed briefly. It is pertinent at this point to call attention to the more prolific workers in this field: Nelson, Moore, Mohr and Turner of Johns Hopkins University; Magnuson and his group at the University of North Carolina; Chorpenning[11a,11b] of the United States Army; Levaditi and his co-workers of the Pasteur Institute; and Durel and his co-workers who were the first in 1951 to report from Europe experiences with the Nelson and Mayer technique.

APPLICATION OF THE T.P.I. TEST TO CLINICAL DIAGNOSIS. Magnuson and Thompson[37] attempted to determine the degree of precision of Nelson and Mayer's technique on large numbers of serums from normal and syphilitic patients and animals and to establish ways in which the method might be modified to permit more convenient assays. The *in vitro* test for immobilizing antibodies against *T. pallidum* as reported by Nelson and Mayer was performed by Magnuson and Thompson on serums of 362 patients with syphilis, 81 patients with disease other than syphilis, 73 normal patients and 91 normal rabbits. No positive reactions were encountered in any of the nonsyphilitic persons. In syphilitic patients the immobilizing antibody developed fairly early in the course of the disease. The incidence of positive reactions increased with the duration of the infection. Modifications in technique were suggested that would permit more extended assays with the same amount of materials. They found that the T.P.I. test is an excellent tool for investigations dealing with immunity and problems involving biologic false-positive serologic reactions but feel that the test requires further investigation.

In another study, Nelson and his co-workers[57] examined the serums from 81 medical students at the Johns Hopkins University whose histories were considered reliable with regard to the absence of syphilitic infection. The serums from 80 of the students were negative for immobilizing activity. Serums from 87 additional patients with diseases other than syphilis were also found to be negative with the immobilization test. All patients in this group were selected as free from syphilis on the basis of a negative history of infection and a negative standard serologic test for syphilis. The clinical diagnosis and the number of cases in each category were as follows: malaria, chronic, relapsing, 8; malaria, acute early, 2; pulmonary tuberculosis, 11; lupus erythematosus disseminatus, 1; infectious mononucleosis, 10; atypical pneumonia, 10; diabetes mellitus, 1; leishmaniasis, 1;

typhoid fever, 2; typhus fever, 1; chancroid 1; lobular pneumonia, 1; lobar pneumonia, 4; scarlet fever, 2; measles, 11; mumps, 2; poliomyelitis, 1; pertussis 1; chickenpox, 3; streptococcal pharyngitis or tonsillitis, 11; Caffey's syndrome, 1; infantile dysentery, 1; and post-vaccination for smallpox, 1. Unsatisfactory tests were obtained with sera from patients with chickenpox, 1; atypical pneumonia, 1; and infectious mononucleosis, 1. The serums from 50 patients with latent syphilis, from patients with asymptomatic neurosyphilis 18, from 51 patients with late symptomatic syphilis and from 6 patients with untreated late congenital syphilis gave strongly positive immobilization reactions. Serums from 7 persons with late syphilis produced strongly positive treponemal immobilization activity, despite the lack of reactivity with lipid antigens of the 3 standard serologic tests used. Quantitative titration of immobilizing antibody was done on 15 serums in each of the following categories: normal, primary, secondary, latent and late symptomatic syphilis. The titers of these serums were expressed as the serum dilution which produced immobilization of 50% of the treponemes after 18 hours' incubation at 35° C., that is, the T.P.I. (18 hours). The 15 normal serums all gave negative reactions. The median titer for the serums of primary syphilis was 60, for the serums of secondary syphilis 810, for the serums of latent syphilis 4,860 and the serums of late symptomatic 4,860. Comparative titrations of the reagin in these serums were performed with the Eagle and VDRL cardiolipin test procedures. There was a general progressive rise in both reagin and immobilizing titers from primary to secondary syphilis. No correlation existed between the two antibody titers in latent and late symptomatic syphilis.

The immobilizing test was performed on samples of cerebrospinal fluid collected from 25 patients with miscellaneous diseases in whom syphilis was excluded. None of the 25 fluids from patients with disease other than syphilis showed immobilizing antibody. Fluids from 19 patients with latent syphilis were also negative; 2 gave doubtful reactions, and 4 gave positive reactions. All 33 fluids from patients with central nervous system syphilis gave positive immobilizing reactions. Serums from 12 patients with presumed biologic false-positive reactions were examined and found to be free of immobilizing antibodies. Additional information regarding the specificity of the immobilization phenomenon indicated that immobilizing antibody was produced regularly as a result of infection with virulent spirochetes of the Treponema groups, namely, *T. pallidum, pertenue* and *cuniculi.* It was not produced in animals experimentally infected with *Leptospira* or *Borrelia* or in animals artificially "immunized" with nonvirulent cultured spirochetes, for example, of the Reiter, Kazan and S-56 strains.

By 1950, Nelson and Mayer's treponemal immobilization test had been sufficiently used to permit review of its status in Canadian[2] and French journals[16]. Further studies involved attempts to increase the sensitivity of the test, the relation of treponemal antibody to probable biologic false-positive reactions, the immunological relationships among species and strains of virulent treponemes as determined by this test, and the relationship between immobilizing and spirocheticidal antibodies against *T. pallidum.*

Thompson and Magnuson[71] studied the effects of varying complement and serum concentration on the sensitivity and specificity of the immobilization test. Their data show that the sensitivity may be materially improved by in-

creasing the concentrations of serum and complement without sacrificing specificity. Nevertheless, a small proportion of patients (2%) with secondary syphilis are still immobilization negative. The immobilization test has been made more sensitive by increasing the final concentration of guinea pig serum from 11.1 to 22.2% simultaneously with an increase in the complement concentration. The authors concluded that the immobilization technique may offer an important tool for the research laboratory in the investigation of problems of immunity in syphilis and in the study of the biologic false-positive serologic reaction for syphilis. However, the reliability and significance of the test need further evaluation.

Nelson and Diesendruck[53] have demonstrated that in experimental animals treponemal-immobilization antibody occurs regularly in the animals infected with organisms of the treponeme group (*T. pallidum; T. pertenue; T. cuniculi*), but not in the animals infected with cultured nonvirulent spirochetes, or in animals inoculated with *Leptospira icterohaemorrhagiae* or *Borrelia novyi*. The treponemal immobilization test was performed by Mohr and his coworkers on 126 sera of patients with treated late syphilis. It yielded positive results in 96.8% of this group. The test yielded positive results in 76.3% of 67 patients with diagnoses of probable latent syphilis. In a group of 63 patients with a diagnosis of probable false-positive reactions, the treponemal immobilization test gave 11% positive reactions. The authors concluded that the treponemal immobilizing antibody is highly specific in the treponematoses, especially syphilis. If treatment was deferred until late in the course of syphilis, treponemal antibody in most instances appeared to persist indefinitely, even though reagin may disappear. Negative treponemal immobilization reactions were obtained in 24% of patients who in the best judgment of the authors probably had late syphilis and in 89% of those classified as biologic false-positive reactors. This suggests that many persons have erroneous diagnoses and treatment for syphilis on the basis of present serologic standards.

Kahn and his colleagues[27] have employed the Nelson and Mayer treponemal immobilization test to study the immunological relationships among the strains of treponemes (those causing syphilis, yaws, and venereal spirochetosis of rabbits, and 4 strains of *T. pallidum*). There was significant cross sensitivity among strains of *T. pertenue*, *T. cuniculi*, and the Nichols strain of *T. pallidum*. Sera from rabbits infected with four strains of *T. pallidum* demonstrated some cross reactivity between each of them and the Nichols strain of *T. pallidum*. There was an absence of immobilizing activity against *T. pallidum*, *T. pertenue*, and *T. cuniculi* in sera from rabbits immunized with Reiter, Kazan, and S-26 strains of nonvirulent, cultivatable spirochetes. Quantitative titrations of immobilizing antibody in sera from rabbits infected with *T. pallidum*, *T. pertenue*, or *T. cuniculi* were performed with homologous and heterologous species of treponemes. Although there was cross reactivity, a definite antigenic difference exists between *T. cuniculi* on the one hand and *T. pertenue* and *T. pallidum* on the other. Similarly, there was a high cross reactivity between 2 strains of *T. pertenue* and the Nichols strain of *T. pallidum*. There was no significant difference between the reciprocal homologous and heterologous immobilizing titers of 3 of 4 strains of *T. pallidum*.

Thompson, Greenberg, and Magnuson[70] note that there is a corresponding loss of infectiousness of virulent *T. pallidum* (Nichols strain) as it is rendered nonmotile by the immobilizing antibody. This relationship is not

directly proportional and suggests that infectiousness may be lost slightly before motility ceases. This non-infectiousness may be due to some alteration in *T. pallidum,* rendering it incapable of reproducing *in vivo,* or it may be that *T. pallidum* is so altered as to render it more susceptible to the natural immune mechanisms of the host. A period of *in vitro* incubation is necessary to demonstrate immobilization and reduction of infectiousness. This suggests either that the initial antigen-antibody reaction was not immediate or that the antigen-antibody complex dissociated *in vivo.* For both the *in vitro* demonstration of immobilization and the *in vivo* demonstration of loss of infectiousness, syphilitic serum in adequate concentration and active complement are required.

In 1951, beside the numerous studies of Levaditi, Vaisman and Hamelin[29], reports by Durel, Sausse, Collart, Poiron and Borel[17] indicated the rising interest of Europeans in the Nelson and Mayer procedure. An editorial in the British Journal of Venereal Diseases[1] outlined briefly the value and potentialities of this method. Demanche[15] also endorsed the procedure. Again Levaditi, Vaisman and Hamelin[33,34] presented a compilation of their experiments, many of which, to be mentioned later, have a distinct bearing on the mechanism of immobilization of spirochetes. From the clinical standpoint, they concluded that in early syphilis, the blood Wassermann becomes negative more slowly than does the result of the Nelson-Mayer test. In secondary syphilis, the lipoidal serologic procedures yield negative reactions well before the Nelson-Mayer reactions become negative. In general, the results in their new report are confirmatory of previously published data.

In 1952, interest in the Nelson and Mayer procedure has become more intense. A compilation of French experience indicates a generally favorable attitude toward it[46,66,69]. Boudin and Blancher[10] use the test as a definitive means of diagnosis of neurosyphilis since a negative result, in his opinion, means absence of neurosyphilis. Merklen and Berthaux[43] found agreement between the Nelson and Mayer technique and the Neurath test, a procedure rarely employed now. Rabut[63], on the other hand, does not believe that so complicated, unreliable and costly a test as the Treponema pallidum immobilization test is necessary. In a well documented detailed and critical response to a previous summary communication by Nelson[50], Touraine[72] feels that although there are decided advantages to be derived from the T.P.I. test, its wide adoption should be withheld until the various difficulties and uncertainties connected with it have been resolved. A somewhat similar doubtful view had previously been expressed by Barnett[3] of the United States who felt that it appears that the T.P.I. test, on account of technical difficulties, is not available for routine use and it is doubtful if it ever will be feasible to utilize it on a very large scale. Although Thivolet[69] had a satisfactory experience with the procedure, he too believed it was a laborious routine with numerous pitfalls. Binazzi of Italy[7] made use of the procedure in a comparative study of syphilitic antibodies in blood, bone marrow and blister fluid.

In Copenhagen, Reyn and Nielsen[65] determined the reagin contents and treponemal immobilizing antibody in 89 sera from 79 patients. Reagins were demonstrated by the following seroactions: Wassermann's complement fixation test as modified by Morch (WR-M); the same, using cardiolipin antigen (C-WR-M), Kahn's standard test (KR) and Meinicke's clarification test (MR). Immobilizing antibodies were demonstrated by Nelson's technique,

which was carefully adhered to; most of the sera were evaluated qualitatively only. The material was divided into three clinical groups: (1) 25 sera from patients with syphilis; (2) 19 sera from clinical doubtful cases and (3) 45 sera from patients in whom the possibility of syphilis could be excluded with almost complete certainty. In Group 1 the reagin and T.P.I. results showed the highest conformity; in Group 2 and especially Group 3 more discrepancies were found. Regarding sensitivity of the T.P.I. test, no definite conclusions could be drawn on the basis of the limited number of sera examined in Group 1. The results confirmed previous investigations showing the high specificity of the T.P.I. test. Durel and his group[17] made a survey of results obtained in the first 1,000 cases, representing a survey of 1,466 tests (many patients had repeated tests). They noted that: (1) *Untreated Patients*: The T.P.I. test is of little value in the diagnosis of syphilis in contacts of cases of infectious florid syphilis, as the diagnosis can best be made by methods already available. In cases of latent infection of long duration, however, the T.P.I. may afford the only proof of infection. The T.P.I. test is especially valuable in patients presenting lesions suspected of being syphilitic, particularly where these suggest late or congenital syphilis. When the serological tests for syphilis are frankly positive or negative, similar results are usually obtained with the T.P.I. test. It is most useful in interpreting intermediate results obtained with the serological tests for syphilis and may detect biological false-positive reactions. (2) *Treated Patients*: The T.P.I. test sometimes gives help in the retrospective diagnosis of a case incorrectly treated as syphilitic. It has great value in judging the part played by syphilis in patients known to have had the disease who present lesions which may be attributable to it. Theoretically it may aid in discriminating between relapse and reinfection, provided that a series of tests have been carried out, a condition rarely fulfilled at present. It has raised doubts about the therapeutic provocation method, the results of which may only be due to biological false-positive reactions. (3) *Relations to Various Forms of Treatment*: Penicillin therapy shows a better negative response with the T.P.I. procedure than the older arsenic and bismuth therapy; the sooner treatment is started, the quicker the action on the T.P.I. The T.P.I. reaction affords a new possibility of establishing cure when it is negative on two occasions; this is open to question, as healing and antibody production are not definitely related. A T.P.I. reaction that remains positive after treatment has no prognostic value. (4) *Comparison with Serological Tests for Syphilis*: Careful quantitative serological tests usually but not invariably agree with the T.P.I. test results. Total positivity of the 2 types of test is more often seen (88.9%) than total negativity (71.4%). Possible causes of discrepancy are discussed. (5) The T.P.I. test shows a few peculiarities in early syphilis: no elaboration of detectable antibodies, delay, "peak" phenomena. (6) The results of the T.P.I. on the cerebrospinal fluid findings in 58 cases are reported. No positive results are found which are not also positive with the serological tests. Frequent discrepancies are found with regard to the Wassermann reaction.

Miller and his co-workers[44] feel that in their experience the treponemal immobilization test proved highly accurate in the diagnosis of human syphilis. Their report was based on 455 patients, composed of 123 individuals with proved syphilis, 250 diagnosed as latent syphilis, and 82 nonsyphilitics. The treponemal immobilization test

was positive at the time it was made, in all proved congenital, central nervous system, cardiovascular, and early latent syphilis; the same was true of gummas. In the group of patients with primary and secondary syphilis, the interval from the time of diagnosis to the time of the treponemal immobilization test varied from 0 to 48 years. Of the 30 patients diagnosed primary syphilis, 4 had negative treponemal immobilization tests; of 39 diagnosed secondary syphilis, 2 had negative treponemal immobilization tests. The negative results occurred in patients who had adequate treatment in the early stages. The test also yielded negative results in 9 instances (5%) of the 213 patients thought to have late latent syphilis. Of these 9 patients with negative reactions to the treponemal immobilization test, 3 had been treated for syphilis more than 30 years previously and their reactions to the serologic tests for syphilis were still fluctuating. Two patients had been treated for syphilis more than 10 years previously, and their reactions to the serologic test for syphilis were positive. The remaining 4 patients had had a diagnosis of syphilis for less than 10 years. In two of these the reactions to the serologic tests for syphilis were becoming negative at the time the treponemal immobilization test was performed. The third patient, with a low titer as determined by the serologic test for syphilis, was not influenced by treatment. The fourth had a very high titer, not influenced by large amounts of penicillin. Every one of the 82 nonsyphilitics had a negative reaction to the treponemal immobilization test. These tests were made on patients with a wide variety of diseases, and would offer opportunity for a false-positive reaction. Miller and his group found none. They did encounter a number of examples of unexpected positive reactions to the treponemal immobilization test; when the patients were confronted with the evidence, an admission of a previous syphilitic infection was obtained in every case.

Miller and his co-workers[45] have also reported their findings on the use of the treponemal immobilization test in 170 patients studied subsequent to their previous report on 455 patients. In 99 patients diagnosed as probable biologic false-positive, the treponemal immobilization test was positive in 3 who had had yaws, and was negative in the remaining 96. The serologic test for syphilis was positive in all of these patients. In another group with a questionable diagnosis of syphilis, the treponemal immobilization test was negative in almost one-half. The authors conclude that the treponemal immobilization test is an extremely reliable test in the diagnosis of human syphilis. According to Moore and Mohr[48], studies at Johns Hopkins University and elsewhere have provided much more information about the treponemal immobilizing antibody, as follows: 1) it does not occur in the serum of normal persons, or of those suffering from nontreponemal diseases; 2) it does occur uniformly in syphilis and the closely related treponematoses, yaws, pinta, and bejel, but not in other spirochetal diseases, such as leptospirosis, relapsing fever, ratbite fever, or Vincent's infections; 3) in untreated syphilitic infections, its rate of appearance in the serum approximately parallels that of reagin; it is first detectable when the primary lesion is from 5 to 15 days old, and rapidly increases in titer for the first few weeks, reaching a plateau at about the second or third month of infection. However, in syphilitic rabbits, it does not decline or disappear from the serum following the spontaneous healing of the chancre, as does reagin; and it is probable (though not yet finally verified) that in man it does not spontaneously decrease in titer with the pas-

sage of years. In patients with untreated syphilis, during and after the secondary stage, it is almost certainly always present for the duration of the patient's life even though reagin may have spontaneously disappeared and the treponemal immobilizing test is therefore a useful diagnostic tool in reagin-free patients, that is, those with negative standard serologic test, with lesions possibly due to syphilis, such as in the differentiation between rheumatic and syphilitic aortic insufficiency. 4) In treated early (primary, secondary, or early latent) syphilis, treponemal immobilizing antibody disappears from the blood as does reagin, but at a slower rate and not necessarily in a parallel manner. Thus, patients treated for early syphilis are usually found, years later, to be seronegative with both tests, though sometimes they are positive for treponemal immobilizing antibody and negative for reagin. 5) In treated late syphilis, that is, of several years' duration, on the contrary, treponemal immobilizing antibody usually does not disappear from the serum, though reagin may do so; and such patients examined from 1 to 35 years after clinically successful treatment of late syphilis of whatever type, are 95 to 98% positive to treponemal immobilizing antibody.

These and other data permit the tentative conclusion that the treponemal immobilization test detects an antibody specific for syphilis and the related treponematoses, and that it may be expected, in a modified form, eventually to replace "standard" serologic tests that depend on lipoid antigens for detection of the nonspecific reagin. Unfortunately, this goal is not yet in sight, though efforts at simplification of the test are in progress and are promising. The treponemal immobilizing test is expensive, and since it is not yet possible to cultivate virulent *T. pallidum in vitro*, its performance depends on the maintenance of a large rabbit colony as a source of supply of living treponemes. It requires the use of sterile serum (or spinal fluid). It is time-consuming, complicated, and subject to numerous technical pitfalls. These difficulties have so far limited its use, largely on an experimental basis, to 6 or 8 laboratories in this country, and it is not yet ready for adoption by the thousands of existing serologic laboratories.

Nelson[51] has recently advocated that for the United States Navy, the Treponemal immobilization test or some future modification of it, serve as a final criterion for diagnosis in patients with "suspected" latent syphilis on the basis of a positive standard reagin test. In patients with positive reagin test, shown to be falsely positive by virtue of a negative T.P.I. test, an extensive effort should be made to determine by medical examination and other laboratory investigation, the factors responsible for the false-positive reagin test.

TREPONEMAL IMMOBILIZATION TEST AND BIOLOGICALLY FALSE-POSITIVE SEROLOGIC REACTIONS. For a long time it has been known that the standard serologic procedures employed in the diagnosis of syphilis produce false-positive reactions due to a variety of diseases and conditions. The available literature on this subject has been analyzed by a number of students[13,5,64,68,47]. To the present, all attempts to devise a specific serologic method for the diagnosis of syphilis have failed. Accordingly, the indication, that the Nelson-Mayer procedure was at last the possible answer to the problem of biologic false-positive serologic reactions, was hailed with intense interest. [Since this material was compiled, comparisons of results of the T.P.I. test and the Neurath procedure or the Kahn verification test, indicate the superiority of the T.P.I. test over the older procedures. (Roy, A. N., Hill, J. R.,

Gowdey, J. L., Kalaec, L. C., and Rein, C. R., Am. J. Syph., Gonor., & Ven. Dis., 37, 338, 1953, and Harrell, E. R., (Jr., Ibid., 37, 330, 1953).] Levaditi and his group[32] felt that the test was of exceptional importance in ferreting out false-positive reactions to the lipoid tests. Gate, Sohier, Thivolet, Saucaz-Larame and Rolland[20] from a study of 47 subjects, feel that a positive T.P.I. result meant syphilis. Olansky and his colleagues in the United States Public Health Service[58] made a preliminary report of apparent biological false-positive reactions in 4 serological tests for syphilis and the treponemal immobilization test. They felt that the T.P.I. test, as performed in their study, showed poor reproducibility but no trend toward an increased number of false reactions in the presence of malaria.

The outstanding presentation indicating the value of the T.P.I. test as a means of solving the biologic false-positive serologic reaction problem is that of Moore and Mohr[48]. According to these authorities, "From the earliest development of the treponemal immobilizing test, it was obvious that its most practical and clinically important use might lie in the differentiation of the positive standard serologic test due, on the one hand, to syphilis and, on the other hand, to the biologically false-positive phenomenon. This is in fact the case. Nelson and his associates have demonstrated that the treponemal immobilizing test was negative in 12 acute biologically false-positive reactors, in whom the false-positive standard test was due to the following causes: primary atypical pneumonia in 6; infectious mononucleosis in 1; malaria in 1; chickenpox in 2; and measles in 2.

"We, on the other hand, have applied the test to the recognition of the much more frequent, difficult, and complicated problem of the chronic biologically false-positive reactor. The validity of the test, under these circumstances, depends on the observation that in treated late syphilis, the treponemal immobilizing test remains positive, presumably for the duration of the patient's life, and in spite of the type or amount of previous treatment.

"Our clinical material consists so far of 300 patients known to be seropositive with standard techniques for 6 months or longer (in some cases, as long as 10 to 15 years), and in whom the diagnosis lay between latent syphilis (no manifestations except the positive serologic test for syphilis) and the chronic biologically false-positive phenomenon. Before the performance of the treponemal immobilizing test, our patients were assigned to one or other of these categories on the basis of the presence or absence of the collateral evidence, outlined in table 2. . . ."

"The results of the treponemal immobilizing test in these 2 groups and in a group of 256 patients with clinically verified late syphilis . . . and the comparison with clinical judgment are shown in table 3. In the category of 'Syphilis, late, treated' the diagnosis in all cases depended on the presence of clinically recognizable lesions of the infection. In those classified as 'probable latent syphilis' or 'probable biologically false-positive reactors,' the clinical diagnosis depended on a verified positive standard serologic test for syphilis, plus, in each case, all or most of the collateral studies outline in table 2."

"From these data, it is suggested that there is a margin of error in both directions, which is probably of clinical judgment rather than of the treponemal immobilizing test, that is, about 15% of patients in whom we had diagnosed latent syphilis were actually biologically false-positive reactors; and 16% of those whom we had thought to be

nonsyphilitic actually had syphilis. Nevertheless, the agreement between clinical diagnosis and the results of the treponemal immobilizing test is remarkably close."

"Other than our own study and some as yet unpublished observations of Nelson in the United States Navy, nothing is known so far of the incidence of chronic biologically false-positive reactors. This information will not be forthcoming until larger scale serologic surveys have been undertaken in which all seropositive reactors with standard tests are checked by the treponemal immobilizing test. A guess may be made however, that the phenomenon is frequent, since in our own practice, 43% of patients in whom in earlier years latent syphilis would have been diagnosed have now been identified as biologically false-positive reactors (table 3)."

"Use of the treponemal immobilizing test permits, for the first time, a definite answer to the question, 'Does this patient have syphilis?' When this question is answered in the negative, however, it is at once replaced by another and perhaps even more serious question: 'What is the cause of the chronic biologically false-positive phenomenon?' The answer to this latter question is not available from the existing literature. Surveys of the incidence of presumed biologically false-positive reactions in this or that population group or in this or that nonsyphilitic morbid process are not valid, because positive standard tests with lipoid antigens have in no instance been checked by the treponemal immobilizing technique (except in the case of leprosy)."

"The etiologic background of the chronic biologically false-positive phenomenon is under study in this clinic, by means of a long term clinical follow-up of such patients. Only preliminary results are so far available, but these indicate that the biologically false-positive reaction is not innocuous, to be dismissed lightly, but is oftener, perhaps usually, a manifestation of serious underlying disease. Outstanding among the conditions so far identified in a substantial proportion of biologically false-positive reactors are the collagen diseases, such as disseminated lupus erythematosus, periarteritis nodosa, rheumatoid arthritis, rheumatic fever, and sarcoid. Further details of these studies will appear later."

THE TREPONEMA PALLIDUM IMMOBILIZATION TEST IN THE STUDY OF IMMUNITY OF SYPHILIS. Although a state of true resistance to reinoculation arises in syphilitic infection[4,77], the mechanism of this immunity is not clear. Attempts to produce active immunity in experimental animals by the inoculation of killed *T. pallidum* have been either unsuccessful or unconfirmed. Since the introduction of specific circulating treponemal antibodies in the serum of syphilitic patients and rabbits by Nelson and Mayer, interest is centered around the significance of this antibody in terms of immunity. In rabbits, it has been demonstrated that during the time when active immunity and immobilizing antibody were both increasing with the duration of the infection, the degree of resistance was slightly parallel with the height of the antibody titer[76]. But, other investigations have demonstrated that there is no necessary dependence between these two factors. In experiments with latent syphilitic rabbits which had been infected for similar lengths of time and then treated, in 1949[36] they had already found that the degree of resistance could not be correlated with the T.P.I. titer to challenge or with the extent of an amnestic rise which followed the challenge. In addition, McCleod and Magnuson[42] noted an immunological relationship between syphilis and yaws spirochetes through cross-immo-

bilization tests. Thus rabbits with experimental yaws developed high levels of no resistance to challenge with small numbers of this organism. The earlier report by McCleod and Magnuson[41], indicating that immobilizing antibodies were produced in mice by the injection of killed Nichol's strain *T. pallidum*, has provided a useful method for study of the mechanisms of immunity in syphilis. McCleod and Magnuson[40] have reported in a more recent contribution, the immunologic response of both rabbits and mice to inoculations of killed organisms. Such injections provoked both a rise in the T.P.I. titer of treated rabbits and the developments of T. P. I. antibodies in normal rabbits, and that these antibodies were present in both rabbits and mice which were not immune to inoculation with universal doses of the homologous strain.

Immobilization reactions have been variously reported in a number of animals infected with other species of spirochetal organisms. Gelperin[22] noted that, in Nelson's hand, serum from group II and III rabbits (II injected intravenously and intraperitoneally with a saline suspension of Reiter's spirochetes, III rabbits received subcutaneous injections of the vaccine in adjuvants) failed to yield evidence of immobilization antibodies to *T. pallidum*, in contradistinction to partial protection observed under these circumstances; this discrepancy may have been the result of differences in sensitivity of the 2 tests, or the cross-reactivity of a virulent strain and a virulent variant, or both. Levaditi and his school have approached the problem of late syphilis by a study of the immobilizing antibodies produced by several spiral organisms[33,34]. The occurrence of spirillicidal, spirillolytic antibodies and opsonins in the serum of animals or humans infested by recurrent spirochetes (*Borrelia duttoni*) was demonstrated many years ago. Levaditi, Vaisman, and Hamelin[34] have demonstrated by the Nelson-Mayer technique specific immobilisins capable of acting against *Borrelia duttoni* in the serum of the mouse, rat, guinea pig and a general paralytic during the course of the involution of the spirillosis. Levaditi, Vaisman and Hamelin[35] found that immobilisin against *Borrelia duttoni* acts on *Spirochaeta hispanica* and that antitreponemic immobilisins are without effect on *Borrelia duttoni*. Levaditi, Vaisman, and Hamelin[34] have also employed the Nelson-Mayer test for identification of strains of *T. pallidum*. Levaditi and his group[84,85] have been unable to induce immunity in rabbits by inoculation of spirochetes devitalized by exposure to ultra-violet irradiation. Nor did these inoculated animals develop immobilizing antibodies. Treatment of syphilitic rabbits with bismuth caused the previously positive immobilization reaction to become negative, leaving the rabbits susceptible to a new infection. Levaditi, Vaisman and Hamelin considered this to indicate that the animal is as receptive to infection as is a new animal.

Some consideration has been given to the question as to whether the immobilizing antibodies affect the virulence of *T. pallidum*. Levaditi, Vaisman and Hamelin[30], employing rats, were able to confirm the previous results, using rabbits, that immobilization of *T. pallidum* implies loss of virulence of the organisms.

Vaisman and Hamelin[79,81] were able to separate by ultracentrifugation at great speed of syphilitic serum the "reagin" of immobilization. The differentiation between the 2 principles shown by chemical and biological means is further confirmed by a biophysical technique. They also employed this technique to separate antityphic agglutinins and antisheep hemolysins

from the immobilization factor, thus distinguishing the antitreponemic immobilisins from agglutinins and hemolysins. Jordan[26] has also demonstrated the separate identities of the Donath-Landsteiner hemolysin (paroxysmal cold hemoglobinuria) and treponemal immobilizing antibody.

TECHNICAL SHORTCOMINGS OF THE TREPONEMA PALLIDUM IMMOBILIZATION TEST. From the presently available information, there is ample evidence that the Nelson and Mayer treponemal immobilization test has great possibilities in many directions in syphilology, but there are still many technical difficulties connected with it. These deficiencies may prevent wide adoption of the procedure. Although certain technical refinements have already been made or suggested[17,54], the greatest problem is providing for an adequate supply of motile, virulent treponemes. To this end, a number of suggestions chiefly in the direction of storage of the organisms at low temperatures[11a,25,39,56], prolonging their survival time by exposure to 5% carbon dioxide and cold temperatures[56]. The immobilization test can be performed with organisms from frozen testis[11a,11b], with results comparable to those obtained with treponemes from fresh syphilomas. The use of cortisone as well as reticuloendothelial blotting methods[52] in experimental syphilis may be adapted to this problem, since infected animals treated with this preparation or methods (Roentgen or nitrogen mustard) exhibit actively motile *T. pallidum* and other spirochetes in considerably larger numbers than are found in control lesions[14,74*]. In spite of the technical shortcomings of the test, continued interest in it in the United States is indicated by the fact that it is still under investigation in at least 7 laboratories[62].

* Increasing sodium thioglycollate in the basal medium and the use of high concentrations of guinea pig complement (Portnoy, J., Harris, A., and Olansky, S., Am. J. Syph., Gonor. & Ven. Dis., **37**, 101, 1953) have improved the performance of the procedure in respect to good survival controls, negative findings with known normal nonsyphilitic serums, a high level of sensitivity, and a few inconclusive findings. Saurino (Am. J. Syph., Gonor. & Ven. Dis., **37**, 112, 1953) also reduced the ambiguous reactions by the use of the modified medium which contained ox ultrafiltrate for enrichment. Durel and his co-workers described a grinder with interchangeable tubes of small capacity for obtaining treponemes for inoculation of new animals (Durel, P., Borel, L.-J., and Sausse, A., Am. J. Syph., Gonor. & Ven. Dis., **37**, 128, 1953). Harris and his group made further evaluation of the quantitative control serums (Harris, A., Portnoy, J., Falcone, V. H., and Olansky, S., Am. J. Syph., Gonor. & Ven. Dis., **37**, 106, 1953).

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PRESENT STATUS OF SURGICAL TREATMENT OF MENIERE'S DISEASE

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SINCE Meniere's original, classic description in 1861[50,51], a great deal has been written about the etiology, the pathology, and the medical and surgical treatment of this disease. The number of theories that have been offered to explain the various aspects of this disease and the conflicting reports regarding the efficacy of the different types of treatment attest both to the complexity of the subject and our present still clouded comprehension of this disease.

The scope of this paper does not permit of any extended discussion of the terms Meniere's disease, Meniere's syndrome or symptom-complex, and pseudo-Meniere's disease. Suffice it to say that the present generally accepted concept is that the term Meniere's disease should be applied only to that group of patients who present a syndrome of vertigo, tinnitus, impaired hearing, nausea and sometimes vomiting, for which no local or systemic cause can be found with any degree of certainty. Previously, patients with episodic attacks of vertigo and nausea or vomiting were diagnosed as cases of Meniere's symptom-complex, pseudo-Meniere's disease and at times Meniere's disease, even though there was no apparent impairment of the cochlear function. Today it seems to be generally agreed that only those patients having tinnitus and impaired hearing in addition to vestibular involvement should be included in this group. Day[20] stresses the fact that signs of cochlear involvement often will precede the vestibular signs by months or years. Reviewing 220 case histories he found only 5 cases with a history of attacks of vertigo preceding the onset of hearing disturbances.

Symptomatology. A brief description of the symptomatology resulting from the vestibular and cochlear involvement should be of value. The most upsetting symptom of this disease is the recurring vertigo. The patient experiences a whirling sensation; either the objects about him appear to be turning or he feels himself to be turning on his own axis, so to speak. This vertigo varies in the suddenness of onset, the intensity and the duration. The vertigo may become more severe gradually or there may be a sudden violent paroxysm. Attempts to move while lying in bed usually produce violent nausea and vomiting. In other cases, the patient is or feels unsteady so that he veers to one side or the

other while walking. Some patients experience a to-and-fro or up-and-down motion. Occasionally, patients are thrown violently to the ground as though struck on the head and then experience severe vertigo, nausea and vomiting. Between "crises" patients are often unable to turn the head suddenly or to lie down or get up from bed without feeling some degree of vertigo or dizziness. In addition to the vertigo there is nausea and often vomiting. Examination during an attack will reveal the presence of nystagmus. This is rotary in type, with a slow and quick component alternating in regular order. It is rarely vertical. The direction of the nystagmus is toward the affected ear if the labyrinth is in the irritative stage of the disease; however, if degenerative changes are present in the affected ear the nystagmus is toward the uninvolved side.

Caloric stimulation of the affected labyrinth (performed between attacks) gives diminished responses as to vertigo, nystagmus, and past-pointing, particularly when testing the vertical canals. In the early stages of the disease normal responses will be elicited occasionally; sometimes, there is diminished caloric response on both sides, but it is more marked on the affected side. Cochlear involvement results in impaired hearing, distortion of sound, with hyperacusis and diplacusis, and tinnitus. The impaired hearing may fluctuate quite suddenly, getting better or worse. Hearing is usually worse after an attack and can improve to a great extent during a lengthy intermission. The low and high audio frequencies are involved and bone conduction is diminished. Because of "recruitment" (a phenomenon in which a "nerve-deafened" ear gains in loudness disproportionately with an increase in the intensity of the sound) these patients suffer great discomfort from loud sounds like subway trains, industrial noises and loud radios. A common finding is the comparatively greater loss of speech comprehension as compared with the degree of pure tone acuity. The tinnitus has a rather characteristic dual tone: a very disturbing low-pitched roar or hum and a less troublesome high-pitched ring.

Meniere's disease is a unilateral process in approximately 80 to 90% of the cases. When it is bilateral the time of onset in the second ear varies; it may appear soon after or not until 4 or 5 years after involvement of the first ear. The hearing loss may be equal to or even greater than in the originally affected ear.

Etiology. The exact etiologic cause or causes of Meniere's disease are not definitely known. A favored theory postulates a dysfunction of the autonomic nervous system or an intrinsic allergy, either of which can lead to a local vasomotor imbalance, especially a vasoconstriction, of the vessels supplying the inner ear. As a result of this vascular change there is an increase in the volume and pressure of the endolymph, which is usually referred to as labyrinthine or endolymphatic hydrops.

Pathology. The common misconception handed down from textbook to textbook and copied by medical paper after medical paper, that Meniere believed hemorrhage into the labyrinth to be the cause of the group of symptoms which he described so well, has been rectified at long last. For this our thanks go to Williams[76] who performed this service by the simple expedient of referring to Meniere's original papers and reading them in the light of Meniere's known ideas about the disease which has been named after him. Williams[76] points out that Meniere was intent on demonstrating to his confreres that vertigo, nausea and vomit-

ing need not necessarily rise from "lesions of the cerebellum or the cerebellar peduncles," but that, "when these symptoms are accompanied by deafness the site of the disease lies in the inner ear." To illustrate this point he presented a case in which a young girl was suddenly attacked by vertigo, nausea and vomiting, and sudden complete deafness. Meniere had seen many instances of "Meniere's disease" and had pointed out the favorable prognosis for life with which the condition is associated. It is clear that he knew very well that patients never died directly from this disturbance, but only secondarily. There is no evidence to show that he intended to imply that this case typified the pathologic background in the particular group of patients he had described.

In 1919, Lermoyez[42] suggested that Meniere's disease must be due to a local angiospasm in persons having an exaggerated susceptibility to external excitants and internal irritants. He stated that one may conceive of a spasm being able to close the internal auditory artery or one of its branches. Closure of the main trunk would affect simultaneously the equilibrial labyrinth and the cochlea resulting in the complete triad of Meniere. Spasm of either one of the branches could lead to vestibular or cochlear symptoms depending upon which branch was involved.

Dandy, as quoted by Green and Douglass[17], felt that the underlying pathology in Meniere's disease was pressure by anomalous arterial loops compressing the eighth cranial nerve. In his series of 607 operations, Dandy noted 85 such loops. His working hypothesis was that Meniere's disease was analogous to trigeminal neuralgia and that a degenerative process in the fibers of the vestibular branch of the eighth nerve was responsible for the symptoms. This, however, was never borne out by numerous histological examinations of parts of the sectioned nerves.

In 1938, Hallpike and Cairns[30] gave a historic paper on the histopathology in Meniere's disease. Histologic sections of the temporal bones of 2 patients, who had previously been operated upon for Meniere's disease by sectioning the eighth cranial nerve, showed a dilated endolymphatic system, with degeneration of the organ of Corti and the stria vascularis, and a pathologic elevation of the otolithic membrane of the utricle. The basic pathology appeared to be a hydrops of the vestibular and cochlear portions of the membranous labyrinth. They postulated that the crisis in the disease did not occur until dilatation of the membranous canal was completed to the full extent of the bony canal. When this was accomplished, any further increase in pressure of the endolymph precipitated a crisis. In 1940, Hallpike and Wright[31] were able to make the same observation in another case. These observations have been confirmed by Lindsay[43] in 1942, and by Altmann and Fowler[3], in 1943. These histologic observations form the basis for the prevailing conception of the underlying pathology in Meniere's disease, namely a hydrops of the labyrinth. It must be cautioned, however, that there is as yet no experimental proof to show that this hydrops is the actual causative agent producing the symptoms of this disease. The possibility that there may be some other factor, with the hydrops merely an accompanying finding cannot be entirely dismissed.

There has been much postulation regarding the endolymph: its flow, its secretion, its resorption, its chemistry and chemical changes occurring during disease. Prevailing opinion seems to be that the endolymph is secreted mainly by the stria vascularis

and is resorbed by the endolymphatic sac and duct. It has been reasoned that an increase in the permeability of the capillary loops of the stria vascularis due to some autonomic dysfunction would result in an excessive increase in the amount of endolymph. Also, it has been theorized that a reduced blood flow in the capillary bed as a result of vasoconstriction would lead to lowered oxygen tension and an accumulation of metabolites with consequent changes in ionic concentration and retention of endolymphatic fluid. Another theory is that the hydrops is due to a disturbance in the sodium metabolism with retention of sodium ions as the underlying causative factor. Still another view is that the condition is basically an allergic problem (Williams): a sort of physical allergy. In short, though the mechanism of the hydrops is not completely understood, the most accepted explanation seems to be that an imbalance of the autonomic nervous system or a sort of intrinsic allergy gives rise to a vasospastic-atonic state of the capillary loops in the stria vascularis resulting in a fluid transudation into the endolymphatic system.

Animal experiments by Lindsay *et al.*[46] to determine the importance of the endolymphatic sac and periotic duct in the traffic of the endolymph showed that the inner ear suffers no histologic or functional injury by losing the services of the endolymphatic sac or periotic duct. They caution that these observations should not be interpreted to indicate that these structures perform no function, but that their function can probably be assumed by other structures in their absence. However, the evidence does show that, in the cat and monkey, obliteration of either the endolymphatic sac or periotic duct is not in itself a cause of labyrinthine disease.

The exact composition of normal perilymph and endolymph is not known. Waltner and Raymond[75] studied five specimens of perilymph from patients with Meniere's disease, collected during the performance of the Day electrocoagulation operation, and one specimen of endolymph obtained during the Portmann operation while tearing the endolymphatic duct. Measurements showed that the protein content of the perilymph and endolymph was identical, but in each case it was more than twice that of the cerebrospinal fluid of the same patients. The sodium content in one specimen of perilymph was found to be similar to that of the cerebrospinal fluid. Of course, it should be realized that the above findings probably represent the end result of the equalization of the osmotic pressure on both sides of the barrier membrane[74] between the endolymph and perilymph spaces. These membranes have been shown to be semipermeable[1] in that they do not permit passage of large colloid molecules, but crystalloids diffuse through them readily. Altmann and Waltner[2] state that under normal physiologic conditions the direction of movement of dissolved substances is from the endolymph towards the perilymph. The assumption is that the hydrops of the labyrinth results from an osmotic gradient in favor of the endolymph.

Because of the lack of positive proof that either hypersecretion or poor resorption of endolymph can be held responsible for the symptoms of Meniere's disease, since there are many inconsistencies between Meniere's symptom complex and the histopathology to which these symptoms are attributed, Lempert[41] reasoned that the cause of the symptom complex might lie in some disease of the vestibular labyrinth. With this in mind he performed a partial labyrinthectomy for the relief of vertigo in 6 consecutive patients

suffering from repeated severe paroxysmal attacks of Meniere's disease. He carefully removed the membranous endolymphatic external semicircular canal including the ampulla in all six cases. Part of the utricle was pulled along with four of these canals. Instead of finding a uniformly smooth inner lining of the membranous semicircular canals, which is observed postmortem in the normal temporal bone, the inner lining of these particular membranous external semicircular canals was invariably found to be studded with vesiculated epithelial excrescences varying in size and number and suggesting epithelial fluid collections. A controlled study on two Rhesus monkeys showed no vesiculation of the biopsied labyrinths. From these findings Lempert[41] and his co-workers postulated that the epithelial vesiculation is pathologically significant in Meniere's disease and that the disease is a chronic progressive herpetic neuritis of the vestibular labyrinth of either toxic or trophic origin. They theorize that symptoms are due to the rupture of the vesicles with release of a toxic fluid into the lumen of the endolymphatic membranous labyrinth. The size and number of vesicles rupturing at one time determine the severity of the attacks. The violent vertigo is due to the hyperexcitability of the crista by the contaminated endolymph and not to the increase in fluid pressure. They assert that the distention in the endolymphatic system is due to excess pressure from vesiculation and toxic fluid production and this pressure, taking the course of least resistance, distends the cochlear duct and bulges or ruptures the delicate Reissner's membrane. They attribute the loss of hearing to progressive damage of the organ of Corti by repeated contamination of the endolymph. The tinnitus is the result of stimulation of the organ of Corti by the contaminated endolymph and the deafness during the attack is due to a toxic loss of function in the hair cells of the organ of Corti. As the contaminated endolymph is absorbed, these symptoms gradually subside. In explaining the symptoms of Meniere's disease they deny any important role to the increased pressure in the endolymphatic system. In the discussion that followed, Williams[78] stated that Lempert's demonstration supported the hypothesis of allergic origin of Meniere's disease, rather than "the very fanciful hypothesis" (of herpetic neuritis). Under the hypothesis of allergic origin, affection of the stria vascularis produces an altered type of secretion of endolymph containing a high concentration of protein with a higher osmotic pressure. This would tend to attract fluid from the perilymph space through the semipermeable membrane of the endolymphatic system. Guild[29] stated that the bleb-like irregularities on the inner wall of the membranous semicircular canals are of common occurrence and that if they are of pathological significance then there were many cases of sub-clinical Meniere's disease in the audience. Shambaugh[69] pointed out that the endolymphatic labyrinth is of ectodermal origin and the vesicular lesions observed by Lempert may be analogous to hives on the skin, the results of an allergic antigen-antibody reaction.

The pathological picture would not be complete without discussing another very interesting facet. Rosen[64,65], while performing the fenestration operation, cut the chorda tympani nerve and stimulated the central end. In 33 out of 36 cases stimulation produced sonic responses variously described as hissing, roaring, buzzing, ringing, and so forth. In 6 cases vertigo resulted from this stimulation.

From all of the foregoing it is apparent that the etiologic and the caus-

ative pathologic factors in Meniere's disease still remain an unsolved riddle.

Treatment. Most of the patients afflicted with Meniere's disease respond quite favorably to various types of medical treatment. Others, however, are either not benefited by this therapy, or it is impractical to employ the required type of therapeutic regimen because of the patient's occupation or economic situation, or the effects of the disease cause so much mental distress that radical treatment becomes mandatory. In such cases surgical treatment has been tried in order to relieve these patients of their attacks of incapacitating vertigo.

The goal of the surgical treatment of Meniere's disease is the elimination of the attacks of vertigo and the relief of the tinnitus, without further impairment of hearing. In addition, the ideal operation should be free from danger to life, be fraught with no serious complications, the operative morbidity should be of short duration, rehabilitation should be quite rapid, and the operative technique should show consistent results and not be too difficult for a well trained surgeon to master.

During the past decade otologists and neurosurgeons have devoted a good deal of attention to the surgical treatment of Meniere's disease, so that there are now a number of operations designed to relieve the intractable vertigo which has failed to respond to medical treatment. In line with their familiarity with the operative field, neurosurgeons have naturally advocated intracranial section of the eighth nerve, while otologists have favored attacking the labyrinth and other otic structures. Nearly all of the operations to be described have been successful in eliminating the vertigo; however, in the relief of tinnitus and preservation of hearing they have had generally poor success.

According to their rationale these operations can be classified into five groups as follows:

1. Dissociation of the affected end organ (labyrinth) from the brain by section of the eighth cranial nerve, either partially or completely.
2. Partial or complete destruction of the peripheral end organ (labyrinth) by various means such as
   a. Injection of alcohol
   b. Electrocoagulation
   c. Avulsion
   d. Removal of the stapes and the membrane of the round window
   e. Plugging the external semicircular canal
   f. Ultrasound
3. Creation of a safety valve to permit the overflow of hydropic endolymph by incising the endolymphatic sac (Portmann's operation) or cutting the endolymphatic duct.
4. Adjusting the upset autonomic mechanism by means of operations on the sympathetic nervous system. (The object is to prevent vasoconstrictor impulses from reaching the membranous labyrinth.)
   a. Injections of procaine into and extirpation of the stellate ganglion
   b. Dorsal sympathectomy
   c. Decortication of the vertebral artery
5. Section of the Chorda Tympani Nerve and Tympanic Plexus (based on a new theory of hearing) as advocated by Rosen.

1. SECTION OF THE EIGHTH CRANIAL NERVE. Dandy stated that in 1874 Charcot[13] made the observation that when deafness in Meniere's disease became complete, attacks stopped spontaneously and he suggested that division of the acoustic nerve might be bene-

ficial. Ballance[5], in 1894, also suggested section of the eighth nerve for the relief of vertigo. Krause was given credit by Frazier[24] with having sectioned the eighth nerve in 1905 for the relief of tinnitus. In 1908, both Frazier[25] and Ballance[6] sectioned the nerve, one for the relief of dizziness, the other for "painful tinnitus". Frazier[26] again performed the operation in 1913 for tinnitus. None of these early operations was apparently attended by great success. It was not until Dandy[15] made his first report of successful results following total section of the nerve in 1928 that the operation of intracranial division of the acoustic nerve for Meniere's disease became accepted and popular. Coleman and Lyerly[14], Cairns and Brain[9], Olivecrona[54], Munro[53], and Walsh and Adson[72] soon followed with reports of successful results from division of the eighth cranial nerve. In 1931, McKenzie[48,49] reported partial section of the nerve in order to interrupt the vestibular fibers, but spare the cochlear fibers. This modification was adopted by Dandy[16,17] who reported performing this operation in over 600 cases in 1945. Following are reports of the results of this operation by various surgeons.

Green and Douglass[28] reviewed Dandy's series of 587 cases in which there were only 2 postoperative deaths due to meningitis. The follow-up showed that a little under 90% of the patients obtained relief from vertiginous attacks, and there was practically no difference in this result whether a complete or partial section of the eighth nerve had been performed. Of 114 patients who had section of the entire auditory nerve on the side of their referred tinnitus only 42 (32.9%) reported complete relief of their tinnitus. This is the relief that was obtained 5 to 20 years after operation, and not the immediate result, which may give a higher percentage. Of the 245 patients who had section of the vestibular fibers only, a smaller percentage (26.8%) were free from tinnitus. Most patients in either group obtained no relief from the tinnitus. So far as hearing is concerned, they estimate that by means of partial section usable hearing (with hearing aids, for example), has been preserved for 40 to 45% of the ears. (However, their figures do not offer positive proof of this estimate.) The most important complication was facial paralysis. This resulted from trauma and fell into two categories, permanent and transient. The transient ones cleared within one month. The permanent paralyses usually appeared immediately or soon after operation and varied from mild partial to complete paralysis. With complete section, 16% developed transient and 9.2% permanent facial palsy; with partial section, 5.8% developed transient and 1.7% permanent paralysis.

Lathrop[38,39] reported that intracranial section of the eighth nerve had been employed at the Lahey clinic on 91 patients during a 13-year period, for the relief of intractable vertigo due to Meniere's disease. Total section was employed in 25 patients; vertigo was completely relieved in 16, unchanged in 4, and 5 patients could not be traced. In the remaining 66 patients section was confined to the vestibular component. Of these 66 patients, 46 were completely relieved of their acute attacks of vertigo, 5 noted no improvement and 13 could not be traced. In general, the hearing of those patients subjected to differential section of the eighth nerve remained essentially unchanged as compared to the preoperative *subjective* loss of hearing. The effect upon the tinnitus was variable, but as a rule this symptom was not benefited by either total or partial section of the eighth nerve. Only one of two fatalities is attributed directly

to the operation. Temporary paresis of the facial nerve occurred in only 2 patients. The average duration of hospitalization was 20 days; in the latter years this was reduced to 14 days. The period of economic incapacitation averaged 81 days. Sequelae were weakness, transient periods of postural giddiness and pain, numbness and discomfort in the operative area.

Ray[63] reports the results of complete nerve section in 30 patients and partial nerve section in 20 patients. All but 2 were completely relieved of vertigo. These two had partial nerve sections and by means of postoperative caloric tests were found to have vestibular fibers still remaining. In one a total division was performed with complete relief of vertigo; the other was unwilling to submit to a second operation. Those patients who had total nerve section obtained complete relief from tinnitus in 30% of the cases, improvement in 40% and no improvement in 30%. In patients with partial nerve division tinnitus was abolished in 15%, improved in 25%, and unimproved in 60%. (His statements concerning the effects of partial and complete section on the residual hearing of these patients do not lend themselves to scientific translation. A.H.N.) One patient, age 62, died from a cerebral hemorrhage on the fifth postoperative day. Four patients developed transient facial paralysis. Nystagmus, blurred vision, difficulty in focusing and occasional diplopia were frequent, early complaints. These soon subsided. The majority of patients resumed their normal activities in from 3 weeks to 3 months after operation.

He concludes that, except when it is especially desirable to preserve hearing, total division of the acoustic nerve has the advantage over partial division in that it is easier to perform, all vestibular fibers are unquestionably cut and there is greater likelihood of obtaining relief from tinnitus as well as vertigo. He feels that patients with hearing already impaired by Meniere's disease do not find deafness in the diseased ear an increased handicap.

Walsh and Adson[72] reviewing their series state that total sectioning results in greater relief from vertigo and also from tinnitus. Yet with complete section of the nerve in 11 cases, there was complete relief from tinnitus in only 2, partial benefit in 2, and no improvement in 7. In those patients who had partial section, when hearing was preserved vertigo was not abolished and when vertigo was abolished, hearing was not preserved.

Castellano[10] (from Sweden) reports the results of section of the eighth nerve in 254 patients; in 27 the entire nerve was cut, in 226 only the vestibular branch was severed. Complete relief of vertigo was obtained in all but 8 patients. Of the 226 patients with vestibular section, 46 became totally deaf, 26 became worse, and in the rest it remained unchanged, except for 5 who improved. Disappearance of the tinnitus was rare with either type of nerve section. Temporary facial paralysis occurred in 14, permanent paralysis in 2 patients. There were no operative deaths.

Barber and Ireland[7] report the results of partial section of the eighth nerve during a period of 20 years, from 1931 to 1951. During this time 117 patients were operated upon. Two died immediately after operation, five died later of unrelated causes. Seven patients had complete section of the eighth nerve. Of the remaining 103 patients with section of the vestibular portion of the eighth nerve, 53 returned for follow-up examinations. Careful determinations of residual hearing were conducted by pure-tone audiometry testing and by recorded speech and masked conversational voice. The results of their long term

follow-up showed that partial section of the eighth nerve gave complete relief from vertigo in 83% of the cases, partial relief in 3.8%. (This is in essential agreement with the reports by Green and Douglass[28] in the follow-up of Dandy's cases.) Tinnitus was abolished in only 4 out of the 53 cases, but improvement was found in 41.5% (compared with 36.9% in the follow-up by Green and Douglass[28]). In general, useful hearing was retained in 26.4%; only 1 patient out of 16 had useful hearing in the 10 to 20 year follow-up, 4 patients out of 19 had useful hearing in the 5 to 10 year follow-up, and 9 out of 18 had useful hearing in the 0 to 5 year follow-up period. This long-term failure of hearing might be explained by the progressive nature of the disease in the labyrinth. Half of the group which showed useful levels by pure-tone test were found to have a significant discrepancy in their reception of recorded speech. This indicates that the final assessment of retained hearing must not be made on the basis of pure-tone audiometric tests alone. Out of 17 patients with serviceable hearing before operation, 11 retained useful hearing after surgery. They conclude that hemisection of the eighth nerve for labyrinthine hydrops offers the patient about 2 chances out of 3 of retaining useful hearing in the operated ear for a period up to 10 years. Eighty-five per cent of the patients were pleased with the results; 5 (9.4%) had failure due to development of hydrops in the unoperated side. They conclude that this operation is satisfactory for the rehabilitation of the patient suffering from severe vertigo due to hydrops of the labyrinth. Improvement of the tinnitus cannot be assured. Useful hearing can be preserved in a good percentage, so that it is the operation of choice for those patients who are deaf in the unaffected ear and for those who have good preoperative hearing on the diseased side. If the preoperative hearing is below the useful level, destruction of the labyrinth and differential section of the eighth nerve are of equal value.

Advocates of this operation assert that although it is a major surgical procedure, it is relatively safe when performed by experienced neurosurgeons. When section has been confined to the vestibular component of the nerve, they maintain that the results obtained approximate the goal of surgery more nearly than any other procedure.

A possible reason for the lack of complete success of partial section is the fact that according to Rasmussen[62] two grossly distinct nerve trunks are found only in a fair proportion of cases. There is rarely a true division into cochlear and vestibular fibers. In nearly all cases there are obvious vestibular fibers in the cochlear trunk. He stated that in one such nerve sectioned, nearly one-fifth of the apparent cochlear nerve was occupied by vestibular fibers. It also appears that if the surgeon tries to make sure that the vestibular fibers are all divided, not enough cochlear fibers would remain in most cases to carry on cochlear function.

Putnam[61] stated that intracranial section of the eighth nerve was neither as easy, rapid, nor safe as some accounts would lead us to believe.

Williams[77] states that Cairns estimated the mortality rate in intracranial division of the eighth nerve to be in the region of 5%, with a rather large morbidity rate due to injury of other closely associated cranial nerves. Although he was one of the earlier neurosurgeons to advocate intracranial division of the eighth nerve in cases of Meniere's disease, he appears to have abandoned this procedure in favor of the destructive labyrinthotomy done by his colleague Cawthorne.

2. DESTRUCTION OF THE LABYRINTH. *A. By Injection of Alcohol.* This method has been employed mainly in England. Wright[81,82,83,84] injected alcohol into the labyrinth through the oval window in 60 patients. There was improvement in the vertigo in 55, failure in 5. Total deafness developed in the operated ear in all patients. Tinnitus was improved in 33 patients. Postoperatively, 2 patients developed facial paralysis; one of these remained permanently. One patient developed meningitis. Mollison[52] injected 3 minims of absolute alcohol into the labyrinth through a fistula in the horizontal semicircular canal in 50 cases. He reported that 74% of the patients were cured of the acute attacks of vertigo, 10% were not improved, and the remaining 16% were either improved or could not be traced. Mollison[52] used this method only when the hearing in the affected ear was poor and in the other ear relatively good. All the patients experienced further loss of hearing in the operated ear after surgery and no postoperative complications were encountered. McDowall[47] employed this method in 22 patients. The sudden severe attacks of vertigo were relieved in 20 patients, but transient postural vertigo on sudden change of position persisted in 7 patients. Two patients could not be traced. Tinnitus was absent in 2 patients both before and after operation; it was relieved in 8 patients, improved in 4, and remained unchanged postoperatively in the remaining 6 patients. There were no postoperative complications.

B. By Electrocoagulation of the Labyrinth. This method has been advocated by Day[18,19]. A partial simple mastoidectomy is done to expose the bony horizontal semicircular canal adequately. Then, through a fistula near the ampullated end of the bony semicircular canal, electrocoagulation of the membranous horizontal semicircular canal and the vestibule is performed. He uses a dental broach followed by a needle electrode to coagulate the sensory nerve endings in the vestibule, because he believes that this procedure insures a smoother and shorter period of convalescence. He advises against the employment of the needle electrode by the inexperienced surgeon since there have been reports of facial paralysis occurring after its improper usage. Day[21] states that he first attempted to perform a differential electrocoagulation of the vestibular contents without destroying the saccule or damaging the cochlea. In this way he succeeded in preserving cochlear function in 16 out of the first 54 patients he operated upon. Four patients had a recurrence of vertigo, including 2 who had retained hearing, due to incomplete destruction of the vestibular labyrinth. Successful revisions were done in these 4 cases. However, in only 4 cases was he able to demonstrate useful hearing 2 years after operation. In the majority of cases loud roaring tinnitus and distortion of hearing persisted, with deafness gradually increasing. Due to the persistent tinnitus, the chances of incomplete vestibular destruction, and the relatively early loss of useful hearing anyway, he decided to abandon the procedure of differential electrocoagulation and now performs a labyrinthectomy with destruction of both the cochlear and vestibular mechanisms by electrocoagulation. Day[21] states his reasons for favoring this operation as follows: It is completely effective in ending attacks of vertigo in unilateral Meniere's disease and relieves distressing cochlear symptoms at the expense of destroying hearing which is of little or no use already. Surgical risks are minimal. In his series of 94 operations the only complications were two simple hematomas. The procedure is relatively

simple and surgical shock is minimal. The operation can be completed in 30 minutes. Several patients over 70 have been operated upon and one patient over 80. Hospitalization requires 7 to 8 days and the average patient is back to work within 3 weeks following surgery.

Lathrop[38,39] reports the use of electrocoagulation of the labyrinth in 20 patients in the Lahey Clinic. Vertigo was completely relieved in all. The hearing in the operated ear which in no case had been at a serviceable level preoperatively was totally lost in all patients. The tinnitus was completely relieved in 4 patients, markedly improved in 10, unchanged in 5, and worse in one patient. There were no deaths. The only postoperative complication was temporary facial paresis which developed in 2 patients. The average duration of hospitalization was 9 days and most patients returned to work within one month after operation. Transient dizziness on sudden change of position, a sensation of giddiness when walking in the dark or a feeling of fogginess in the head occurred in half the cases, but disappeared within 3 months.

Lathrop[38] states that this procedure has been employed by other otologists. Sullivan[70], in Canada, operated on 15 patients with success in 11 and failure in 4. The latter were re-operated and the remaining portion of the membranous horizontal semicircular canal was avulsed with complete relief from vertigo. House[33] performed 5 such operations. The tinnitus and vertigo were relieved in 2, improved in 2, and made worse in one patient. Johnson[35] performed 3 such operations with complete relief from vertigo, but the tinnitus persisted and hearing became worse. Bateman[8], in England, employed this procedure in 4 patients with resulting freedom from vertigo in all. Transient facial paralysis developed in one, while hearing improved in another.

Krech and Harris[36] report the relief of vertigo in all of their 12 cases treated by electrocoagulation. The hearing was further diminished in all cases and for the most part the tinnitus was unimproved. There was no facial paralysis, no postoperative complications and the average hospital stay was 6 days.

Frenckner[27] states that in Sweden the electrocoagulation method has been abandoned more and more, owing to the risk of damage to the facial nerve.

Lindsay[45] remarks that Day's more favorable experience suggests the possibility of some variation in technique, such as his stated practice of withdrawing the coagulating tip slightly after it has impinged on the wall of the vestibule, before applying the current.

In order to obtain additional information about the histologic changes following intralabyrinthine electrocoagulation which might be of value when the preservation of hearing is an important consideration, Altmann and Montreuil[4] operated the 12 ears of 6 Rhesus monkeys, with a strictly aseptic surgical technique, followed by daily injections of penicillin. They conclude from their postoperative findings that in the cases in which a coagulating current of lower intensity was used the changes were confined to the area of the fenestra and its immediate vicinity. When the intensity of the current was somewhat higher atrophy of the crista ampullaris was observed, sometimes combined with residua of a serous labyrinthitis. They reasoned that the atrophy of the crista could be the direct effect of the coagulating current, the serous labyrinthitis the result of a chemical irritation following a more extensive coagulation necrosis of the labyrinthine contents. One possible way of avoiding serous labyrinthitis

seemed to be a reduction in the intensity of the coagulating current. However, they report that this theory did not hold in the case of a man with Meniere's disease who developed a labyrinthitis with complete loss of hearing following electrocoagulation with a low current. They conclude that reducing the intensity of the coagulating current is not an effective way of achieving an elimination of the vestibular function with preservation of hearing. On the other hand even strong coagulation currents will sometimes be insufficient to abolish the vestibular function entirely, as happened in one of their patients who was operated upon twice and yet retained some vestibular function which caused attacks of dizziness. They also caution that if the current is too strong facial paralysis can ensue.

They conclude that the vestibular portion of the labyrinth, due to its proximity, shows the main damage. The electric current itself, or the heat created by it, causes necrosis of certain parts of the membranous labyrinth. This is followed by secondary reparative changes in response to the tissue necrosis, by the ingrowth of organizing connective tissue, which might go far beyond the area of the original necrosis and fill up the lumina of the semicircular canals and the greater part of the vestibule. Later, bone might be formed within the connective tissue. The extent and degree of the changes within the vestibular portion seem to depend mainly upon the intensity of the electric current used, provided that no infection supervenes to complicate and confuse the picture. Thus, if the currents are weak, the changes are confined to the vicinity of the opening in the semicircular canal.

Interpretation of the changes in the cochlea is much more difficult. This is mainly due to the invariable postmortem changes in the organ of Corti and the inability, in many instances, to differentiate between these postmortem changes, fixation artefacts, and intravital changes which, although morphologically insignificant, might nevertheless cause a complete loss of function. The only thing which seems certain is that even without a supervening infection the coagulation necrosis is followed by a diffuse serous aseptic labyrinthitis. The degree of the remaining or returning cochlear function depends upon the extent to which the damage, suffered by the cochlear structures from the labyrinthitis, is permanent and irreversible. No correlation could be found between the amount of this damage, the intensity of the coagulating current, or any other factors. In an attempt to reduce the intensity of the postoperative serous labyrinthitis, the strength of the coagulating current was reduced in various degrees in 2 cases of Meniere's disease. The result, however, was unsatisfactory since the dizziness was not completely eliminated, but the hearing was nevertheless completely lost.

From these studies they conclude that in the cases of Meniere's disease in which coagulation is indicated a strong current should be used and a postoperative infection prevented by use of antibiotics. The small size of the window and its location away from the ampulla might also reduce the amount of postoperative reaction. Any attempt to decrease the intensity of the coagulating current in order to preserve the hearing is useless and jeopardizes the elimination of the vertigo. In order to prevent damage to the facial nerve, excessively strong currents should also be avoided. In view of the many variable factors, the operator must be guided in the selection of the proper strength of the coagulating current by his personal

experience and his familiarity with the method used.

Schall and Rambo[68] working with monkeys concluded that where optimal current is used the damage to the vestibular mechanism is unpredictable and that retention of serviceable hearing is improbable.

C. By Avulsion of the Membranous Labyrinth. Avulsion of the membranous horizontal semicircular canal has been perfected by Cawthorne[11], in England, for the surgical treatment of intractable labyrinthine hydrops. Instead of electrocoagulating he effects the same result by avulsing the membranous horizontal semicircular canal and the contents of the vestibule. Removal of these minute structures is accomplished with small forceps while observing the fistula in the bony horizontal semicircular canal through a binocular loupe or dissecting microscope, but it is greatly facilitated by the use of a medium sized dental broach rather than a forceps. This operation always results in total and irreversible loss of both cochlear and vestibular function of the ear operated upon and is reserved for those cases that are thought to be unilateral and in which the cochlear function is already severely impaired. Cawthorne[12] reported 159 cases, in 152 of which the cochlear and vestibular function of the operated ear was abolished. Seven patients could not be traced, 140 of the remaining 152 patients were improved and able to work following operation, while 12 were not improved and could not work. The only postoperative complication encountered was secondary infection of the wound, which occurred in 2 cases. There were no fatalities in this series. Cawthorne[12] stated that the 140 patients who were able to return to their former occupations usually were able to do so in well under 2 months.

Otologists in Canada and this country have utilized this operation in fewer cases and have obtained similar results. Lathrop[38] reports that Sullivan[70] has employed this procedure for the primary surgical treatment of Meniere's disease in 44 cases since 1938 and has obtained relief from vertigo in 43 of the patients. One patient required re-operation, at which time remnants of the saccule and utricle were removed. This patient has since been free of vertigo for 6 months. He has also avulsed the membranous canal in 4 patients in whom he had previously electrocoagulated the labyrinth, because of recurrence of the vertiginous attacks. Following removal of the remaining portion of the membranous canal these patients have likewise been free of vertigo. One postoperative death occurred in this series as a result of a cerebellar abscess. The average period of hospitalization in this series has been 7 days. These patients have been sufficiently rehabilitated in 3 or 4 weeks following operation to permit nonmanual work, while those patients doing manual labor required 4 to 6 weeks for rehabilitation. Ireland[34], after reviewing 33 of Sullivan's cases for a paper on the diagnosis and treatment of Meniere's symptom complex, concluded that "destruction of the labyrinth is perhaps equally effective (as resection of the vestibular fibers of the eighth nerve) but should be performed by an otologist familiar with minute ear surgery."

At the Lahey Clinic, Lathrop[38] reports, avulsion was employed in 5 patients. In each instance the vertigo was entirely relieved and definite improvement in the tinnitus was noted except for one patient. The hearing was totally lost in all 5. There were no postoperative complications.

D. By Aseptic Fibrosis of the Endolymphatic Labyrinth, According to

the Method of Lempert[40]. Finding that destruction of the vestibular portion of the labyrinth of monkeys, when performed under sterile precautions, did not result in degeneration of the rest of the endolymphatic labyrinth and the organ of Corti, Lempert[40] reasoned that partial destruction of the vestibule, therefore, cannot be expected to relieve the tinnitus. When the organ of Corti and the endolymphatic labyrinth do degenerate after partial destruction of the vestibule, it is only because of postoperative infection. However, in such a case, the tinnitus is not relieved, and is even perpetuated by the cochlear neuritis which results from the extension of the inflammation from the organ of Corti to the cochlear nerve trunk. He, therefore, concluded that in order to relieve both the vestibular and cochlear symptoms a technique must be found to result in degeneration of the entire endolymphatic labyrinth which would prevent the recurrence of endolymphatic hydrops. Furthermore, this degeneration must not be the result of excessive postoperative inflammation or infection.

The basic procedure is the removal of the stapes and round window membrane, permitting the perilymph to drain out. This is done without traumatizing either the temporal bone or the endolymphatic labyrinth. Sterile precautions are taken and penicillin is given. This results in aseptic degeneration of the entire endolymphatic labyrinth and of the organ of Corti.

He reports that of 10 patients who were operated on with this technique, 9 were freed from both vertigo and tinnitus; the tenth had no vertigo, but did have some, though diminished, tinnitus. Because of the minimal postoperative inflammatory reaction, he states that the convalescence was rapid and not too uncomfortable.

E. By Plugging the Lateral Semicircular Canal. Lempert, at a meeting of the American Academy of Ophthalmology and Otolaryngology in Chicago, October, 1949, made a preliminary report that by plugging the lateral semicircular canal attacks of dizziness were eliminated, at least during the time of observation, while hearing was preserved. Altmann and Montreuil[4] found that on histological examination of 3 ears of monkeys where the fenestra was plugged with bone chips the changes in the fistula and adjacent areas were essentially the same as in the cases with electrocoagulation. These findings encouraged them to try this procedure in 3 patients with Meniere's disease. From their results in these 3 cases they conclude that plugging of the horizontal semicircular canal may or may not eliminate the vertiginous attacks, no matter whether the vestibular findings indicate "utricular paresis" or "canal paresis." Even though done with the greatest aseptic precautions and followed by adequate antibiotic therapy, the plugging was always followed by a diffuse serous labyrinthitis, as manifested by the complete, though temporary, loss of auditory and vestibular functions. In 2 cases some of the hearing returned, but it was far below the serviceable level. The vestibular function returned, at least partially, in 2 cases and in the third there was a recurrence of vertigo necessitating complete destruction of the labyrinth. They conclude that plugging of the lateral semicircular canal is not an effective method for the surgical treatment of Meniere's disease, since it is not reliable either for the elimination of vertigo or the preservation of serviceable hearing.

F. By the Use of Ultrasound. Krejci[37] reports experiments using ultrasound applied to the inner ear of guinea pigs. He was able to destroy vestibular function without much

loss of cochlear function. This treatment was given one patient with resulting elimination of vertigo and tinnitus which had persisted when checked 11 months later. Facial paralysis, which occurred after the treatment, had cleared almost completely. There was some loss of hearing.

Wiethe[75a] states that, since direct surgical intervention on the labyrinth is difficult and not always satisfactory, he used high-frequency sound waves, the oscillations being over 300,000 hertzian (electric) waves per second, in the treatment of 26 patients with Meniere's syndrome. He felt that the advantage of this treatment lay in the possibility of pinpointing the structures of the labyrinth and modifying the frequency of the sound wave so as to obtain a varying therapeutic effect. The treatment was given every day or on alternate days for an average of 10 doses. Follow-up observations from 2 to 12 months after treatment showed 18 patients to be completely free of attacks of vertigo; 6 had occasional episodes and in 2 there was no change. The tinnitus was relieved in 9 patients, improved in 10 patients and unchanged in 5 patients. Audiometric studies showed some hearing improvement in 6 patients and no change in 20 patients. Caloric and rotatory tests showed only slight changes.

3. CREATION OF A SAFETY VALVE. Creation of a safety valve to permit the overflow of hydropic endolymph by incising the endolymphatic sac (Portmann)[57,58] or tearing the endolymphatic duct at the point of its emergence from the petrous pyramid (Woodman)[79].

In 1927, Portmann[57,58] advocated opening the saccus endolymphaticus for Meniere's disease, and claimed good results. This operation was conceived before the pathological process was known. The discovery by Hallpike and Cairns of a hydrops of the labyrinth in Meniere's disease seemed to strengthen Portmann's thesis that drainage of the saccus is a logical procedure.

The operation is performed through a postaural mastoid incision and the mastoid opened in order to expose the lateral sinus. By blunt dissector and fine curette, the cerebellar dura medial to this is lifted from the posterior surface of the temporal bone.

In 1939, Woodman and Stirk Adams[80] reported 10 cases in which they performed the Portmann operation, 9 of them with striking results. In 1952, Flett[23] reported his results in 61 cases operated during a 10-year period up to 1949 by the Portmann method, as follows: Perfect results 14; improvement 36; immediate failures 8 (in any case that shows no immediate improvement destruction of the labyrinth is performed one week later); postoperative deaths 2; wrong diagnosis one. Of the 36 cases with improvement, vertigo disappeared in 21, was improved in 12 and unimproved in 3; the tinnitus was gone in 11, was slight in 7, unimproved in 10; hearing was normal in 6, no improvement or worse in 30. Flett[23] states that he has performed no destruction of the labyrinth since 1947.

Lindsay[44], in 1947, reported the results of his experiments with monkeys in which the saccus was incised and various degrees of destruction of the ductus endolymphaticus were performed. From these experiments he concluded that the maintenance of a normal volume of endolymph is not dependent upon a functioning ductus endolymphaticus or even upon its existence. Also the occurrence of a hydrops or Meniere's disease cannot be attributed to interference with normal absorption of endolymph from its dilated and convoluted middle portion. Moreover, drainage and partial destruction of the saccus was followed

by sealing off and healing of the defect without any demonstrable effect on the labyrinth beyond, so that he reasoned that any effect of Portmann's operation on Meniere's disease would be of relatively brief duration.

Altmann and Montreuil[4] suggest that closure of the drainage opening could possibly be prevented by placing the opening into the labyrinth itself thus draining the endolymph into the perilymph, instead of into the subarachnoid space. This could be effected by excision of a small piece of the lateral semicircular canal. The two openings in the membranous canal might be kept patent by the flow of endolymph toward the perilymphatic space. They suggest that the window in the lateral semicircular canal be made into the vertex of its convexity, as far as possible away from the vestibule. In this way the danger of a postoperative labyrinthitis and its damaging effect on hearing would be considerably reduced. The window in the bony canal should be closed with an inert, non-irritating material and great care should be taken to leave the width of the lumen of the canal unchanged. (So far no reports have appeared citing actual experience with this procedure. A.H.N.)

4. REGULATION OF THE UPSET AUTONOMIC CONTROLS BY OPERATIONS ON THE SYMPATHETIC NERVOUS SYSTEM. *A. Stellectomy and Dorsal Sympathectomy According to the Method of Passe.* Passe[55] states that, in 1947, he first considered the hypothesis that neurovascular disturbances, resulting from an underlying autonomic imbalance, could be the etiological factor in a large number of cases of Meniere's disease. He recalls that Portmann and Despons[60] found that there was hyperexcitability of the labyrinth after administration of drugs which stimulated the sympathetic and hypoexcitability after administration of depressor drugs. Portmann stated that "it is definitely agreed that vasodilatation produces hypoexcitability and vasoconstriction hyperexcitability." Terracol[71] stated that there was no doubt that the autonomic nervous system has a definite influence on the function of the inner ear. The cerebral blood vessels are supplied with sympathetic vasoconstrictor fibers and parasympathetic vasodilator fibers. Stimulation of the cervical sympathetic produces a reduction in the caliber of the intracranial vessels. This vasoconstriction may involve not only the internal auditory artery, but also the posterior inferior cerebellar artery and bulbar arteries thus affecting the brain stem at the region of the cochlear and vestibular nuclei, and so on. In abnormal states of the intracranial vessels Passe[56] states that it is more than likely that the labyrinthine vessels can go into spasm, producing an initial hyperexcitability of the labyrinth. Variability in the size and distribution of the cochlear and vestibular arteries could account for the predominance of vestibular or cochlear symptoms in the event that vasoconstriction plays a major role in the production of Meniere's disease.

Because of these considerations, Passe[56] felt that the approach to this problem was sympathectomy. In his earlier cases he interrupted the sympathetic distribution of postganglionic fibers to the head and neck by stellectomy, with, he states, very encouraging results. In his second series of cases, preganglionic section was performed, but evaluation of the results proved to be too difficult. He used stellate ganglion block with 1% procaine hydrochloride as a diagnostic test in the selection of cases. An interesting occurrence is the rapid dilatation of the blood vessels of the tympanic membrane, also of the conjunctiva. He further notes that injection of the su-

perior cervical ganglion or stellate ganglion after dorsal sympathectomy also results in dilatation of the tympanic vessels. Injection of the second, third and fourth thoracic ganglion gives dilatation of the tympanic vessels without Horner's syndrome if thoracic "one" is avoided. After stellectomy, injection of the second, third and fourth paravertebral ganglia did not produce dilatation of the tympanic vessels. It would thus seem that there are vasoconstrictor fibers for the head and neck in thoracic "one", though most arise from the second, third and fourth thoracic ganglia.

According to Passe[56] the technique of sympathetic block is relatively simple and can be easily performed in a few minutes. The patient is ambulatory immediately afterward. He cautions that the use of epinephrine in the procaine hydrochloride must be avoided and that the injection must not be made into a vessel or the spinal theca of a nerve root. The patient's hearing is carefully tested audiometrically before, 2 minutes after and again 10 minutes after the injection. If the tinnitus is diminished or relieved entirely and there is also an audiometric improvement in the low tones for air conduction, then the case is considered suitable for sympathectomy. He stressed that selection of the cases is a matter of absolute importance and immediate improvement must be adequate before conditions are considered suitable for sympathectomy. It was also noted that after stellate block the speech discrimination is improved more strikingly than the pure-tone gain, suggesting that the disturbance in Meniere's disease is not confined to the periphery, but involves the whole auditory projection pathway. This he considers to be of extreme diagnostic and prognostic significance.

During the performance of a stellectomy using the standard anterior approach, Passe also strips the vertebral artery. The technique used in upper dorsal sympathectomies is that described by Smithwick, except that Passe decentralizes only the second and third ganglia, instead of the second, third and fourth.

His results in 45 cases treated by stellectomy are given as follows: Vertigo was completely relieved in 28, improved in 16, unchanged in one; tinnitus was completely relieved in 11, reduced in 23, unaltered in 11; hearing was improved in 32, unchanged in 13.

His results in 46 cases treated by upper dorsal sympathectomy are as follows: Vertigo was completely relieved in 28, improved in 16, not traced 2; tinnitus was completely relieved in 9, improved in 19, unchanged in 16; hearing was improved in 38, unchanged in 6, not traced in 2.

A comparison of the results of the two procedures shows that relief of the vertigo was equally good in both, but stellectomy gave better results in relieving the tinnitus and improving the hearing. Against this advantage, however, is the occurrence of a Horner's syndrome with stellectomy, which women may find to be a cosmetic detraction. His stellectomy cases cover a period of 5 years, the upper dorsal sympathectomy 2 years.

It should be cautioned that arteriosclerotic patients are never subjected to this operation because of the danger of thrombosis of the posterior inferior cerebellar artery; also, the operation is never performed bilaterally.

Lathrop[38] reports the use of stellectomy in 3 patients with Meniere's disease at the Lahey Clinic. He states that while the operation is theoretically simple, it presents troublesome technical pitfalls. Two of the 3 patients obtained relief from the vertigo the other did not; the effect on hearing could not be determined. All 3

developed a Horner's syndrome which they found annoying.

Altmann and Montreuil[4] report failure to obtain sufficiently satisfactory results following stellate ganglion injection with procaine or alcohol to justify extirpation of the ganglion.

Hoogland[32], in Holland, states that ablation of the stellate ganglion has given poor results because the resulting dilatation disappears after a few days and cannot be reproduced. On the other hand, blocking of this ganglion with 20 cc. of 0.5% procaine without epinephrine allows repeated relief from vasospasm. He treated 27 patients with vertigo, tinnitus and auditory impairment by this technique. The more serious cases were given stellate blocks twice a week at first, and at longer intervals later. In bilateral cases injections were given on alternate sides. Rarely were more than 10 blocks necessary. The results were immediate improvement in 22, no improvement in 5. Late results were: vertigo improved in 20, unimproved in 6; tinnitus improved in 9, unchanged in 7; hearing improved in 6, unchanged in 16. He concludes that stellate blocks are effective and should be tried before destructive procedures are undertaken.

5. SECTION OF THE CHORDA TYMPANI NERVE AND TYMPANIC PLEXUS AS ADVOCATED BY ROSEN. According to Rosen[65,66], this procedure is based on a new theory of hearing, the essence of which is that there are two sonic systems in man: one, the more recent cochlea, and two, the older, primitive sonic system derived from the lateral line organ of aquatic vertebrates. In these primitive animals the seventh and ninth cranial nerves carry the sonic and equilibratory impulses to the brain stem. The chorda tympani (seventh cranial) and tympanic plexus-Jacobson's nerve (ninth cranial) are derivatives of this primitive system and both enter the geniculate ganglion. The chorda tympani nerve at the geniculate ganglion is a continuation of the nervus intermedius (nerve of Wrisberg), and the nervus intermedius communicates with the vestibular branch of the eighth cranial nerve (the newer sonic system) in the internal auditory canal (Cunningham's Anatomy). Thus the old sonic system (seventh and ninth nerves) is connected with the newer sonic system (eighth nerve) via the geniculate ganglion and via branches of the tympanic plexus-Jacobson's nerve to the oval and round windows. Thus, if and when these primitive sonic and equilibratory nerves, seventh (chorda tympani) and ninth (tympanic plexus-Jacobson's nerve), are affected, then impulses arising in the tongue, jaw-joint, teeth, pharynx, tympanum and sinuses could stream toward the geniculate ganglion, thence via the nervus intermedius to the eighth nerve, or through the branches of Jacobson's nerve to the oval and round windows to give rise to capillary spasm, and ultimately endolymphatic hydrops. The clinical picture of Meniere's disease would result.

Surgery consists merely in sectioning the chorda tympani nerve, alone or together with the tympanic plexus-Jacobson's nerve. The operation is performed through an ear speculum in the external auditory canal, under local anesthesia and mild sedation. A complete circular incision is made through the skin over the bony canal wall 5 to 7 mm. external to the drum. The skin is then separated from the bone as far as the drum. The drum is then lifted out of its sulcus and reflected upward upon itself like an apron, thus exposing the tympanic cavity. In half the cases the chorda tympani is quickly visible for about 4 to 6 mm. close to the edge of the posterior bony canal. In the rest it has to be teased out

into the tympanum from just behind the bony edge of the canal wall. It is then engaged in a small iris hook, pulled outward and cut. Jacobson's nerve and its branches are scraped away from the promontory of the tympanum and sectioned with a sharp dental hoe excavator which removes the often bone-imbedded nerves.

The chorda tympani was stimulated with three kinds of electrical stimulation both before and after sectioning and the results were essentially the same with all three types of stimulation. In 36 consecutive cases stimulation produced no taste sensation, but taste perception disappeared on the anterior two-thirds of the tongue on the same side after section of the nerve. In all cases stimulation caused facial contraction. In 33 of the 36 cases stimulation of the chorda produced sonic responses variously described as hissing, roaring, buzzing, ringing, and others. In 6 cases vertigo resulted from chorda stimulation. Rosen[66] states that theoretically the taste system in man would include within it a sonic and equilibratory system which has been passed down from aquatic vertebrates. This may explain the sonic and equilibratory effects observed on stimulating the chorda.

He reports the results in 14 patients operated upon by the technique he describes. Of these, 11 patients have had no vertigo since surgery, in 2 vertigo persisted. Tinnitus disappeared in one patient, was improved in 7 patients, and unchanged in 6 patients. Hearing was not destroyed in any of the patients. The procedure is simple, is performed under local anesthesia and requires only 2 to 3 days of hospitalization. It can be performed safely on both ears in cases of bilateral Meniere's disease. Rosen urges that it be tried before resorting to destructive labyrinthotomy. He[67] cites an interesting observation. Two of his patients developed severe Meniere's disease following complete destruction of their labyrinths on one side; in one it was secondary to mumps, in the other due to a fracture of the petrous pyramid. Sectioning the chorda tympani nerve in both cases abolished the vertiginous attacks.

Frenckner[27], writing from Sweden, states that although vertigo is often abolished by destructive operations on the labyrinth, the tinnitus is usually unchanged and hearing is usually partly or completely destroyed. When the hearing is worthless, it does not matter, but when it is relatively good it is highly undesirable to have to sacrifice it.

His procedure is 1) to relieve intralabyrinthine pressure through the fenestration operation; 2), to destroy the vestibular function without injuring the membranous labyrinth, by tamponade of the vestibule and the ampullar portion of the horizontal semicircular canal, thus preserving cochlear function; 3), to reduce or abolish the tinnitus by means of a tympanosympathectomy, section of the chorda tympani nerve, and the tensor tympani and stapedius tendons.

This operation was performed on 13 patients, all with advanced, severe cases of Meniere's disease. The results were completely satisfactory in respect to vertigo and tinnitus. Hearing was retained in most cases, although it deteriorated as a result of the operation. Patients were hospitalized for 2 to 4 weeks after surgery. The observation period has varied from 9 months to 2 years.

Conclusions. The foregoing enumeration and description of the many types of surgical procedures and the various philosophic approaches must have certainly impressed the reader with the present magnitude of this problem.

The goal of surgical therapy in this disease is the consistent and perma-

nent elimination of the vertigo and tinnitus with preservation or improvement of hearing. Coupled with this, the ideal surgical procedure should be free from danger to life, fraught with no serious complications, entail little operative morbidity, permit rapid rehabilitation, and be not too difficult for a well trained surgeon to master. So far, this ideal has not been discovered, but in the light of these requirements it may be easier to evaluate the surgical procedures available at this time.

Until relatively recently (some 12 to 14 years) partial or complete section of the eighth cranial nerve was considered to be the operation of choice in this disease. This was due not only to the great influence of Dandy who had reported using this operation in more than 400 cases and in whose hands it was made to appear comparatively simple, but also to the fact that there was no other time-tested procedure available. Since then, the freedom from fear of meningitis, which has been bestowed by the sulfa drugs and antibiotics, and the increasing technical skill that otologists have acquired in the surgery of the labyrinth and contiguous structures, have led them to attempt to solve the enigma of this disease (pathologic as well as therapeutic) by an otologic approach, which would seem inherently to be the right approach. Before proceeding to evaluate the various operative procedures, it should be cautioned that because remissions of the symptoms are a characteristic of this disease, the true results of the more recent promising treatments can only be assessed after they have been tested in the crucible of time. Another point to remember is that evaluation of a procedure must be based not merely on the claims of its originator, but, more important, on the experiences of other workers using the same operation.

Bearing the above criteria in mind, the choice of surgical intervention in Meniere's disease boils down to three main procedures that have consistently given relatively good results over an extended period of time in the hands of a number of workers. These are: section of the eighth nerve, avulsion, and electrocoagulation of the membranous labyrinth. The significant results from the 3 operations are as follows:

1. Vertigo is eliminated equally well with all 3 procedures.

2. Tinnitus is unchanged in the majority of cases with all 3 procedures, but is more likely to be improved by destruction of the labyrinth than by differential section of the eighth nerve.

3. Hearing is more likely to be preserved by differential nerve section than by destruction of the labyrinth, but there is always a risk of recurrence of vertigo, because of the danger of leaving some vestibular fibers intact. Also, the hearing usually becomes progressively worse anyway. Differential electrocoagulation is unreliable and has been abandoned by its originator, Day, who asserts that retention of distorted hearing is more of a disadvantage and is not desired by the patients.

4. The incidence of permanent facial paralysis is greater with nerve section (up to 4%) than with avulsion or electrocoagulation. However, in hands other than Day's, electrocoagulation carries with it a not inconsiderable danger of permanent facial paralysis.

5. Comparing formidability of operation, operative morbidity and mortality, and duration of convalescence, the choice is overwhelmingly in favor of destruction of the labyrinth.

In choosing between avulsion and electrocoagulation, the lower morbidity of the latter is outweighed by the higher incidence of facial paralysis. Therefore, generally speaking, avulsion of the membranous labyrinth would appear to be the procedure of

choice for the usual case of severe Meniere's disease. Some exceptional instances are these: In unilateral involvement where hearing is still good, or when there is deafness on the uninvolved side, and in cases of bilateral involvement, differential section of the eighth nerve may be indicated in order to preserve hearing. Even here, it is a question as to whether the chance of preserving the hearing, about one out of 3 or 4, offsets the mortality and morbidity rates of the intracranial operation.

Judgment regarding Lempert's operation in which he removes the stapes and round window, will have to be reserved until reports of this procedure by other workers become available. His pronounced success should be an incentive to others to test this method.

Incision of the endolymphatic sac and section of the duct has met with indifferent success generally, except at the hands of the originator and Flett in England. Other workers have stated that success is only temporary. This can readily be understood from the experiments of Lindsay which showed that the incised sac sealed over rather quickly and no demonstrable effect on the labyrinth could be seen.

Passe's reports of excellent results following stellectomy and upper dorsal sympathectomy unfortunately have not as yet been corroborated. Lathrop states that the operation is not as simple as it sounds and in only 2 patients out of 3 was the vertigo relieved; all 3 developed an annoying Horner's syndrome. Hoogland reported poor results because of the disappearance of the vascular dilatation after a few days and his inability to reproduce it. On the other hand, he reports good results by repeated blocking (up to 10 times) of the stellate ganglion with procaine hydrochloride without epinephrine. Further reports will have to be awaited before proper conclusions regarding the efficacy of his procedure can be drawn.

The procedure described by Rosen, based on an intriguing new theory of hearing, is relatively simple to perform; and if his reported success can be duplicated it holds out much promise of meeting the largest number of requirements to date for being an ideal operation in this disease. It would seem well worth trying before resorting to destructive labyrinthotomy.

Summary. A review of the present status of surgery in Meniere's disease has been presented. An attempt has been made to make it comprehensive enough so that the reader may have a sound basis for independent judgment of a highly complex problem which is still far from satisfactory solution.

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BOOK REVIEWS AND NOTICES

THIS IS YOUR WORLD. BY HARRY A. WILMER, M.D., PH.D IN PATH. Pp. 165; illustrated. Springfield, Ill.: Charles C Thomas, 1952. Price, $5.50.

THOUGH this is a book written primarily for professionals working with the tubercular patient, much of its content could be applied to any chronically ill patient. The main portion of the book deals with the many difficult emotional problems encountered in tuberculosis. It gives an understanding of psychological aspects involved and offers the trained worker methods to help his patients understand the implications of their disease. Drawings, both dramatic and humorous, supplement the text.

Group therapy by means of recordings, ballads, dialogues, and realistic talks to patient groups are discussed. Emphasis is placed on the importance of not arousing anxiety in the tubercular patient.

Here is a sound, constructive book that should be of help to those many workers seeking more knowledge of the conflicts disturbing tubercular patients.

O. E.

NUTRITION IN THE PRACTICE OF MEDICINE. With Comments on Nutrition, Disease and Geography. BY J. ARNOLD BARGEN, PAUL R. CANNON, JOHN B. CONDLIFFE, PERRY J. CULVER, ROBERT M. KARK, HEINRICH NECHELES AND FREDERICK J. STARE. Pp. 163. New York: The National Vitamin Foundation, Inc., 1952. Price, $1.50.

THIS volume represents the Proceedings of the 4th Symposium on Nutrition held at the University of California in October 1951, arranged by Dr. T. L. Althausen and his associates. It is a very successful attempt to give the practicing physician the latest information on nutrition as applied to the practice of medicine. The subjects covered are factors concerned with intestinal absorption, nutrition in relation to liver disease, to ulcerative colitis, tissue devitalization and maintenance, and the influence of pancreatic insufficiency on nutrition. In addition, there is a very interesting discussion by Dr. Paul R. Cannon on tissue changes induced by nutritional deficiencies and to complete the symposium, a discussion on Some International Aspects of Nutrition.

This reviewer wishes to congratulate the National Vitamin Foundation on making this interesting and stimulating volume available to the medical profession at a very nominal fee ($1.50). The practicing physician has found it difficult to keep up with the maze of nutritional information and research findings that have appeared in the various scientific journals, particularly in the interval since the start of the Second World War. In order to make this knowledge available to the practicing physician, the National Vitamin Foundation has been sponsoring a series of nutritional symposia at various universities of which the present volume is the proceedings of the 4th symposium. Although all of the presentations are well written and authoritative, this reviewer is particularly impressed by the discussions on the Nutritional Aspects of Liver Disease in Man, by Dr. Robert Kark, and Nutritional and Metabolic Disturbances in Ulcerative Colitis, by J. Arnold Bargen. This volume is filled with important and stimulating material and is highly recommended to the physician and graduate student.

M. W.

PSYCHISCHE KOMPONENTEN DER SINNESORGANE. BY PROF. DR. BERNHARD RENSCH. Pp. 200; 27 ills. Stuttgart: Georg Thieme Verlag, 1952 (Grune & Stratton, Inc., U. S. agents). Price, DM 22.50.

THE author supports the thesis that the various senses are experienced at least for the most part in the sense organs, and that these organs are the seat of the sensations and the ideas (images) of these sensations. He considers the problem more from the standpoint of a philosopher than of a biologist. Emotions, he maintains, do not run parallel to processes in the cortex but to processes in the sense cells of the nerves.

The brain neurones associate sensations and images by conduction of stimulations and of bringing about consciousness of a self. Since processes of volition can be reduced to special associative processes they do not need a special psychophysical substratum. We are really, he says, imaging with the brain, as the sense organ. There is little doubt that the spatial relationship concerned with touch, temperature, and taste occur in the sense organs. Smell occurs as fusion of the sensations of touch and taste; the same holds true with modifications in the cases of hearing and vision. Antidromic ex-

citations may account for certain ideational pictures and certain hallucinations.

The author points out that anencephalic monsters showed reactions to stimuli of taste, sound, and light, and that animals showed sense reactions after appropriate brain operations, and learned to walk after spinal operations. An eye transplanted to the back in a tadpole produced normal retinograms and other signs of activity in the frog. Some patients with central deafness still have auditory sensations.

These and other pertinent illustrations are used by the author to sustain his thesis. For instance, he attempts to account for the phenomenon of phantom limbs. He states that his thesis may be maintained from either the standpoint of associational psychology or that of "Gestalt." He believes that certain illusional (graphic) figures are produced not by the lines themselves, but by the surfaces confined by these lines.

While the English summaries of the German text have been very helpful indeed in the preparation of this review, the poor English used in them needs interpretation. Despite this and the heterodox nature of the author's hypothesis, the thesis needs careful consideration since the neurone theory is still not accepted, at least without modifications, especially among psychologists.

M. M.

BATTLE CASUALTIES. By GILBERT W. BEEBE, PH.D., Division of Medical Sciences, National Research Council, and MICHAEL E. DE BAKEY, M.D., Professor of Surgery, Baylor University College of Medicine. Pp. 277; 38 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $10.50.

THIS volume presents an exhaustive analysis of data from official records and reports of the U. S. Army Medical Service during World War II, by authors eminently qualified and experienced. There is detailed correlation between the circumstances attending the military action and the resultant casualty. There are excellent statements of logistic problems, of personnel, hospitalization and evacuation. It is not the purpose of the volume to discuss the surgical management of battle casualties, but rather to assist medical planners in a better estimation of needs for special personnel and supplies, and to suggest fields for research to reduce mortality and to improve the management and disposition of casualties. The book should be extemely interesting and valuable to all medical service personnel of the Armed Forces. It should be a text for all officers with planning responsibilities.

R. K.

SURGICAL APPLIED ANATOMY. By SIR FREDERICK TREVES. Revised by LAMBERT CHARLES ROGERS, V.R.D., M.D., M.Sc. F.R.C.S. 12th ed. Pp. 553; 206 ills., 66 in color. Philadelphia: Lea & Febiger, 1953. Price, $6.50.

THE usefulness of Surgical Applied Anatomy first written by Sir Frederick Treves, one of the best known and most successful of English surgeons in the nineties, has proven its usefulness by the fact that it has passed through twelve editions. The last three editions have been revised and edited by Lambert Charles Rogers, Professor of Surgery at the University of Wales. Various editions of this book have appeared for almost seventy years and before 1906, 40,000 copies had been sold. As in earlier editions, an attempt is made to discuss anatomy as it is concerned in actual dealings with disease. The apparent small size of the book is quickly dispelled when one peruses the closely packed 553 pages of illustrations and written material. Included in this edition are 206 figures, 66 of which are in color. The illustrations are somewhat diagrammatic but are concise and clearcut. Professor Rogers occasionally gives opinions which might be considered controversial such as his universal advocation of the Billroth I operation for the treatment of peptic ulcer, and, of course, the entire field of applied anatomy would take several volumes to be covered in detail. All in all, the book is an interesting and useful discussion of a subject dear to the heart of the general surgeon and is well worth the price of $6.50.

G. R.

BASEDOW'S DISEASE. By H. SATTLER, M.D., Prof. of Ophthalmology, Univ. of Leipsig. German-English Translation by G. W. and J. F. Marchand. Pp. 605, 1 ill. New York: Grune & Stratton, Inc., 1952. Price, $10.00.

THIS is an extremely interesting and valuable contribution to the literature on thyroid disease. The author has summarized all the publications pertaining to the thyroid gland from 1722 to 1909 and included 3210 references. Although these papers were written before the physiology of the thyroid was understood, the clinical descriptions including the fate of untreated hyperthyroidism make this a book which should be in the library of every worker in the field.

W. P.

DAS INSELSYSTEM DES PANKREAS. *Entwicklung, Histobiologie und Pathophysiologie mit besonderer Berücksichtigung des Diabetes Mellitus.* BY PROF. DR. HELMUT FERNER, Apl. Professor at Anatomical Institute of the University of Hamburg. Pp. 186; 54 ills. Stuttgart: George Thieme Verlag, 1952. Price, DM 29.70.

THIS excellently illustrated monograph on the "Insular System of the Pancreas in Man" covers the development of the islands and their structure in infants as well as adults. Quantitative data, including discussion of the alpha and beta cell ratio, are provided. There is a brief discussion of insular adenomas. The author hypothesizes the existence of two insular hormones, insulin coming from the beta cells and glukagon coming from the alpha cells, and regards glukagon as a glycogenolytic hormone which increases blood sugar. He also suggests that alpha cells occur in the intestinal mucosa.

The final chapter of the book is devoted to a discussion of diabetes. A short section is devoted to differential staining techniques adapted to the differentiation of the island cells.

The author regards the beta cell system for insulin output, largely controlled by the parasympathetic system; the alpha cells for glukagon production, under the sympathetic nervous system. S. W.

THE JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, R. D. LILLIE, Editor-in-chief, National Institutes of Health; Volume 1, Number 1; January, 1953. Pp. 86; 50 photomicrographs, and 17 graphs, tables, and structural formula. Baltimore: Williams & Wilkins Co., bimonthly, at $7.00 per volume within and $7.50 outside the U. S. and the postal union; $1.50 for single copy when available.

THIS periodical, the official journal of the Histochemical Society, is a greatly needed addition to the list of scientific publications. It promises to serve as a focusing point for advances in fields related to the rapidly growing young sciences of histochemistry and cytochemistry. The material may be of interest to the histochemist, cytochemist, cytologist, histologist, oncologist, biochemist, and the more progressive pathologist. The bacteriologist, too, may find here material applicable to his field.

The editorial staff consists of ten men prominent in the field of histochemistry, who have diverse primary qualifications constituting a well-balanced group. Photomicrographs are numerous and are reproduced with great clarity.

In criticism, it is hoped that the editor will, in the future, avoid references to tables not published in the journal (see the article by Lillie and Burtner, P. 14, references to tables A-E).

Judging by Volume 1, Number 1, the Journal is recommended. C. R.

CLINICAL ALLERGY. BY FRENCH K. HANSEL, M.D., M.S. Pp. 1005; 86 ills., 3 color plates. St. Louis: C. V. Mosby Co., 1953. Price, $17.50.

THIS volume is intended to be a complete text on the subject of clinical allergy. Although written by one who is primarily a rhinologist, it, nevertheless, presents a fairly well-balanced coverage of the subject. The space and emphasis devoted to the upper respiratory aspects of the subject are quite pardonable. By reason of his long interest, research and practice in this field, the author has given a very complete presentation, including numerous references to and citations from the work of many others. At times, he has been too gentle in the handling of such material that is controversial or that has not been generally confirmed and accepted. The book should prove very useful to all with more than a casual interest in the field. The format is convenient; the illustrations are numerous and very well done. R. K.

THE HISTORY OF AMERICAN EPIDEMIOLOGY. BY C.-E. A. WINSLOW, DR. P. H., WILSON G. SMILLIE, M.D., JAMES A. DOULL, M.D., and JOHN E. GORDON, M.D. Edited by FRANKLIN H. TOP, M.D. Pp. 190; 9 ills. St. Louis: C. V. Mosby Co., 1952. Price, $4.75.

SPONSORED by the Epidemiology Section of the American Public Health Association, this interesting volume presents a splendid survey of the story of American epidemiology. The first chapter by Doctor Winslow covers the colonial era and the first years of the republic, when there was "no epidemiology" but an abundance of epidemics. The second chapter by Doctor Smillie deals with the period of great epidemics in the United States from the yellow fever outbreak in Philadelphia in 1793 to 1875, just before the beginning of modern bacteriology. The third chapter by Doctor Doull is on the bacteriological era from 1876 to 1920. The last chapter by Doctor Gordon "Yesterday, Today and Tomorrow" discusses recent developments and current and future

problems. Each writer brings to his task not only a commanding knowledge of his field but a facile pen. The result is an extremely interesting historical survey. R. K.

THE HYPERSENSITIVE MIND. By GABRIEL LANGFELDT, M.D. Pp. 147. Copenhagen: Ejnar Munksgaard, 1951.

THE author starts in with a worthy theme, namely the sensitivity of the human mind. In his title, he promises to say something about prevention and treatment. In his recognition of the sensitive mind, he feels that this is partly hereditary and partly due to environmental influences. He does not seem at all sure as to where one leaves off and where the other begins. After mentioning the fact, however, that family experiences have a great deal to do with whether the mind becomes hypersensitive or not, he goes on to show how mind sensitivity and hypersensitivity shows itself in neurotics, psychopaths, and psychotics. Case histories are given. There is little organization to the observations which are made.

The author disappoints us in his final chapter on Prevention and Treatment when he says, "Quite generally it should be emphasized that individuals disposed to hypersensitive reactions should keep themselves in a physically healthy condition taking necessary respect to the usual mental hygiene rules, fresh air, exercise, sufficient sleep, and avoiding any type of intoxication especially that of alcohol and narcotic drugs." He also recommends Vitamin B_1 and electro-shock therapy. In fact, he is quite enthusiastic about the latter.

The hypersensitive mind is an important subject, but the author if he is consistent, must proceed in his thesis to psychotherapeutic and sociological discussions as part of the therapeutic endeavor. Here is where the treatise falls down. The therapeutic advice is neither modern, nor according to the present consensus, effective. O. E.

MEDICAL CLINICS OF NORTH AMERICA. PHILADELPHIA NUMBER, NOVEMBER, 1952. Pp. 362; illustrated. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00 per annum.

THIS is a Philadelphia number and includes 28 articles, all on pediatric subjects. Some of the topics are the pediatric health examination, the first day of life, the management of the premature infant, retrolental fibroplasia, immunization procedures in private practice, antibiotics in pediatric practice, encephalitis, rheumatic fever, congenital heart disease, hydrocephalus, hernias in infants and children, the deaf child, cancer in childhood, and certain endocrine disorders. They are all highly practical and timely presentations. R. K.

1952 YEAR BOOK OF PEDIATRICS. Edited by SYDNEY S. GELLIS, M.D. Pp. 423; 112 ills. Chicago: Year Book Publishers, 1952. Price, $5.50.

WITH the year 1952, the Year Book of Pediatrics has undergone a change in editorship. The book sustains the same high quality enjoyed in previous years. The selections from pediatric literature between June, 1951 and May, 1952 have been wisely chosen and editorial comment is appropriate and interesting, adding a good deal to the value of the compilation.

Pediatricians and others who care for children will find this a valuable reference work. V. V.

RHEUMATIC DISEASES. By EUGENE F. TRAUT, M.D., F.A.C.P. Assoc. Clin. Prof. of Med., University of Illinois. Pp. 942; 192 ills. St. Louis: C. V. Mosby Co., 1952. Price, $20.00.

THIS textbook consists of 51 chapters of which 8 are written by 10 co-authors in such fields as psychiatry, pathology, dermatology, ophthalmology, roentgenology and orthopedics. It brings together a great deal of the accepted facts concerning the rheumatic diseases and, in this respect, is written from a comprehensive point of view. The author aims to meet the needs of the general practitioner as well as to produce a source of reference for the rheumatologist.

The book is well illustrated and printed. The chapter arrangement of the section dealing with treatment could be improved. The author's presentation of the role of cortisone in the management of rheumatoid arthritis would seem to be colored by enthusiasm rather than mature, long range perspective. His remarks concerning gold therapy indicate a lack of personal experience with this type of treatment.

The emphasis on vaccine therapy is not in accord with modern trends of thought and no proof is given to support the author's claims for the value of vaccines.

The chapters on manipulation and medicolegal features of rheumatism are worthwhile additions. The handling of physical modes of therapy is in general superior to that of the purely medicinal aspects of therapy. J. L.

ANNUAL REVIEW OF MEDICINE, VOLUME 3. Edited by WINDSOR C. CUTTING and HENRY W. NEWMAN, Stanford University School of Medicine. Pp. 442. Stanford, California: Annual Reviews, Inc., 1952. Price, $6.00.

THE third volume of the Review has generally maintained the high standard of its predecessors. The sections are all written by recognized authorities in the field concerned. Each subject is discussed in the light of contemporary literature and the author's special knowledge. This approach obviously tends to enhance the value of the work. Nevertheless, some omissions and errors of interpretation are still encountered. For example, on page 256 are reviewed articles dealing with the technique of the heterophile agglutination test for infectious mononucleosis. Reference is made to a study of cold agglutinins in patients with the disease, but the reviewer fails to indicate whether the presence of cold agglutinins was determined for sheep or human erythrocytes. The major point of another article which clearly shows that erythrocytes from different sheep may give widely different titers with a given serum specimen appears to have been missed by the section's author.

However, the overall value of this as well as the other chapters greatly outweighs these relatively minor criticisms. C. Z.

CARDIAC THERAPY. By HAROLD J. STEWART, M.D. Cornell University Medical College. Pp. 622; 68 ills. New York: Paul B. Hoeber, Inc., 1952. Price, $10.00.

THIS new text is a comprehensive treatment of the medical, surgical, dietetic and psychological aspects of therapy of cardiac disease. The therapy advocated is modern but conservative. The author's personal evaluation of different modes of treatment is wisely included. Thus, the book is not a compendium but a well written, practical and detailed guide to cardiac therapy. W. S.

ADVANCES IN MEDICINE AND SURGERY. GRADUATE SCHOOL OF MEDICINE OF THE UNIVERSITY OF PENNSYLVANIA. Pp. 441; 43 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $8.00.

FROM time to time the Graduate School of Medicine of the University of Pennsylvania has offered short integrated review courses to provide an appraisal of current medical knowledge. Well received by the profession, they have become an annual event. The present volume is in answer to a request for a printed record of these practical and well planned presentations. There are 53 papers grouped under ten headings: The Present Status of Adrenal Cortical Hormones; The Role of Potassium in Health and Disease; The Newer Aspects of the Medical and Surgical Treatment of Hypertension; The Pre-operative Evaluation and Preparation of Patients; Thrombo-embolism; Pulmonary Infections; The Relief of Pain; Current Status of the Cancer Problem; Recent Developments in Viral Diseases; and Functional Disorders (however, the commonest of functional disorders, allergy, is not mentioned). The material is well selected and well presented. The book should be very useful to all general practitioners and to most specialists in clinical fields. R. K.

BLOOD CLOTTING AND ALLIED PROBLEMS. TRANSACTIONS OF THE FIFTH CONFERENCE, JANUARY 21 AND 22, 1952. Edited by JOSEPH E. FLYNN, M.D. Pp. 368; 148 ills. New York: Josiah Macy, Jr. Foundation, 1952. Price, $4.95.

THIS is a verbatim report of the latest of a series of conferences on blood clotting and allied problems. Informative chapters deal with the newer anticoagulants, new clotting factors, defects of hemostasis produced by whole body irradiation, and the fibrinolysin—antifibrinolysin proteolytic enzyme system in blood. There is also an appendix in which is discussed the synonymy of the nonprothrombin plasma factors involved in the conversion of prothrombin to thrombin. Those interested in this complex and rapidly expanding field will find this volume as valuable as its predecessors. C. Z.

KLINISCHE UND SPRACHWISSENSCHAFTLICHE UNTERSUCHUNGEN ZUM AGRAMMATISMUS. By PROF. DR. MED. F. PANSE, DR. PHIL. G. KANDLER AND DR. MED. A. LEISCHNER, all from the University of Bonn, especially from the Institute for Head-injuries. Pp. 72. Stuttgart: Georg Thieme Verlag, 1952. Price DM 6.00.

THIS brochure, the result of collaboration between physicians and a speech expert (Kandler) is Part 48 of the publication "Arbeit und Gesundheit." "Agrammatism" has to do with defects in the joining together of words, groups of words and sentences, affecting also the particles and flexion forms of speech. There is presented a case of agrammatism in a soldier who had acquired a typhus

fever encephalitis associated with hemiplegia, and, at first, complete motor aphasia. The brochure contains a complete analysis of the patient's agrammatism with the literature and the consideration of other forms of agrammatism, such as, for instance, the childhood form. In the authors' case they state that they were dealing with a primary amnestic manifestation. In this case "Gestalt" viewpoints had little to offer in the way of gain. They suggest a revision of the terminology of the subject of aphasia. M. M.

GYNECOLOGY. DISEASES AND MINOR SURGERY. Compiled and edited by ROBERT J. LOWRIE, M.A., M.D., F.A.C.S., D-OG, Associate Clinical Professor of Obstetrics and Gynecology, New York Univ. College of Medicine. Pp. 806; 775 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $22.50.

THE first of two volumes of *Gynecology* is devoted to a presentation of basic information concerning the development, diagnosis and management of the various gynecological conditions. The treatment is divided into twelve sections which include anatomy, physiology and embryology in addition to discussions of individual specific diseases. An unusual feature is inclusion of practical chapters which ordinarily are not found in gynecologic texts. One of these is on Physical Therapy in Gynecology in which the application of heat, massage, exercises, packs, baths, and others, to gynecologic treatment is discussed. All medications which might be useful in the management of gynecologic lesions are tabulated; the manufacturer, packaging details and potency for each being indicated. Minor gynecologic surgical procedures such as biopsy, hymenotomy, cul-de-sac aspiration, culdoscopy and cauterization are described and illustrated in detail.

The text is well-illustrated with black and white and color photographs, line-drawings and photomicrographs, all of which are clearly reproduced. The subject material is outlined with page references at the beginning of each chapter and the general index is complete.

The material, prepared by 70 contributors, has been well edited and arranged by the editor and should prove of greatest value to the practicing gynecologist or to the general practitioner. This first volume is a complete encyclopedia of office gynecology and ought to occupy a prominent place in the active library of those who frequently must solve the problems presented by the female patient. J. W.

POST-GRADUATE LECTURES ON ORTHOPEDIC DIAGNOSIS AND INDICATIONS, VOLUME IV. BY ARTHUR STEINDLER, M.D., Prof. of Orth. Surg., State University of Iowa. Pp. 318; 338 ills. Springfield, Ill.: Charles C. Thomas, 1952. Price, $9.75.

THIS latest volume by Dr. Steindler is divided into two parts. Part 1 is concerned with arthritis and diseases of muscles, bursae, tendons and fascia. Part 2 concerns itself with deficiency and degenerative diseases of the locomotor system. Each section can be considered excellent. In the opinion of the reviewer, this text should be, and will be, useful to the internist and those interested in metabolism, as well as to the orthopedist. All aspects on the problems of arthritis are well covered, and are readily understandable so that I feel certain that the general practitioner will do well to have this text as a part of his library. The section on osteochondritides is well covered and since these occur in growing bones, it becomes apparent that the text will also have value to the pediatrician. The material throughout this volume is very well organized. The illustrations are excellent as well as abundant.

From what has been said, it is evident that this text has a broad, clinical spectrum and should be on the shelf of any physician concerned with the clinical practice of medicine. A. S.

DIE KÖRPERLICHEN BEHANDLUNGSVERFAHREN IN DER PSYCHIATRIE. BAND 1: DIE INSULINBEHANDLUNG. BY DR. MAX MÜLLER, Professor of Psychiatry, University of Bern. Pp. 295; 4 ills. Stuttgart: Georg Thieme Verlag, 1952 (Grune & Stratton, New York, U. S. Agents). Price, DM 36.00.

THIS is a very systematic, detailed, and thorough presentation of the subject of the use of insulin in the treatment of psychiatric patients. It is by Max Müller, who presided at the First International Meeting on the Modern Treatment of Schizophrenia, in Muensingen, Switzerland, 1937, at which the great extension of insulin and convulsive therapies was demonstrated (Kalinowsky and Hoch). While Kalinowsky and Hoch's book presents in English some of the information here set forth, their presentation is by no means so comprehensive, since it also includes other physical methods of treatment. Full attention is given to the technique of administration, the various phases of the shock and the lighter and the severer complications. Contraindications are fully considered as well as combinations of the various physical treatments.

The psychophysiology as well as the psychopathology of the procedure are stated as well as the accompanying psychotherapy. Statistics as to immediate and as to permanent results are set forth, as well as prognosis of cases under treatment, the special indications for this form of treatment in non-schizophrenic disorders, and the theory of insulin's mode of action.

In fact this book is an excellent *vade mecum* and reference volume for any psychiatrist who is administering insulin treatment to mental patients. The author proposes to follow it with a consideration of other methods of physical or chemotherapy in these mental disorders.

M. M.

MEDICAL CLINICS OF NORTH AMERICA, CHICAGO NUMBER, JANUARY, 1953. Pp. 293; 32 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $15.00 per annum.

THIS is a Chicago number and is devoted primarily to a symposium on Gastrointestinal Diseases. Topics include functional diseases of the stomach and colon, gastric hemorrhage, peptic ulcer, gastritis, carcinoma of the stomach, cirrhosis of the liver, liver physiology, hepatitis, diseases of the biliary tract, diseases of the spleen, pancreatitis, Meckel's diverticulitis, regional enteritis, ulcerative colitis, office proctology and an additional article on hypoglycemia. As usual the material has a broad, practical application not only for the general practitioner but for those in specialized fields as well.

R. K.

PRACTICE OF PSYCHIATRY. BY WILLIAM S. SADLER, M.D., F.A.P.A.: Pp. 1183. St. Louis: C. V. Mosby Co., 1953. Price, $15.00.

THIS is the second revision of a comprehensive book on psychiatry by the author. The first book, called the THEORY AND PRACTICE OF PSYCHIATRY was published in 1936. First revision was called MODERN PSYCHIATRY and appeared in 1945. In the present volume, Dr. Sadler has introduced a new feature in the form of a section dealing with what he calls "the attitudinal pathoses." He has also enlarged the section on psychological testing and has devoted a section to psychosomatic medicine. In this volume, as well as in his last, he suggests that the practice of psychiatry be called the practice of personology.

"The pathoses," is a term which the author applies to a group of preneurotic disorders. He says, "a relatively harmless attitude can be converted into a pathosis through ignorance, lack of information, misinformation, prejudice, superstition or tradition. As examples he cites: (1) bad reaction to loss; (2) bitterness over fate; (3) brooding over disappointment.

Dr. Sadler makes his own classification which does not follow the latest classification of the American Psychiatric Association. Many types of personalities are discussed in an interesting way. However, the book is somewhat lacking in the dynamic approach. Dr. Sadler's originality of approach leads to some diffusion of concept and could not be recommended for one wishing the more modern psychodynamic approach to the understanding and treatment of psychiatric illness.

O. E.

TREATMENT OF MENTAL DISORDER. BY LEO ALEXANDER, M.D. Pp. 507; 143 ills. Philadelphia and London: W. B. Saunders Co., 1953. Price, $10.00.

THIS is a comprehensive book on the many treatment approaches to psychiatric disorders. The writer's experience has made him unusually well equipped to present the various chemical, as well as electric and insulin shock, treatments. The treatment techniques are well described and there are many explanatory illustrations. Of particular interest to some readers will be the discussions of the theory of the changes which bring about cure as well as the discussion of complications and fatalities due to physical treatment methods.

The psychodynamic approach is well presented also but the amount of space devoted to physical treatments would leave the reader to assume that a great deal more concern should be given to chemical and physical treatment methods than is currently being practiced. As a reference book for chemical, physical and shock treatments it is unexcelled.

O. E.

PAIN SYNDROMES AND THEIR TREATMENT. BY JAMES M. TARSY, M.D., Chief, Arthritis Clinic, New York Post-Graduate Hospital. Pp. 592; 266 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $12.00.

THE subject matter of this book is confined to the diagnosis and management of painful, central-nervous system and connective tissue system disorders of the neck, shoulder and upper extremity. The problems are approached from the point of view of disturbed anatomy as seen by the orthopedist and neurosurgeon. The differential diagnosis of the numerous syndromes occurring in this region

is fully presented in an orderly and logical fashion. In treatment the emphasis is almost exclusively on physical measures, such as heat, physical therapy in general, manipulation, regional anaesthesia, nerve blocks, and so forth.

The book thus brings together those facts which are pertinent to the rheumatologist in the diagnosis and management of upper extremity syndromes from the fields of anatomy, orthopedics, neurology and regional anaesthesia. The volume is well written, illustrated and indexed and should find a useful place as a source of reference on the mechanical aspects of rheumatology. J. L.

DANGER SIGNALS. By DR. WALTER C. ALVAREZ, Emeritus Consultant in Medicine, Mayo Clinic. Pp. 176, Chicago: Wilcox & Follett Co., 1953. Price, $3.00.

THIS reviewer does not know whether the publication of "Doctor Books" at the lay level is a good thing or a bad thing. If they are undesirable, then nothing can be done to prevent their publication. Since their publication is, therefore, inevitable, it is important that they should be written by mature and authoritative medical men. Dr. Walter C. Alvarez fulfills these requirements eminently and, in addition, has the virtue of writing in a concise and interesting manner. His book "Danger Signals" is an excellent and comprehensive summary of medical information, written in exceedingly simple language, which should be a useful guide on health matters to all persons of stable personality. Unfortunately, the anxious and neurotic individual, as Dr. Alvarez admits, may only succeed in feeding his anxiety by reading this or any other type of medical literature.

J. L.

A MANUAL OF CLINICAL ALLERGY. By JOHN M. SHELDON, M.D., Professor of Internal Medicine, ROBERT G. LOVELL, M.D., Instructor in Medicine, and KENNETH P. MATHEWS, M.D., Assistant Professor of Internal Medicine, all in the University of Michigan Medical School. Pp. 413; 27 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $8.50.

THE authors of the manual in their preface state that it was prepared for the physician interested either primarily or secondarily in allergy and its practice. In that respect it has accomplished its purpose. It credits its readers with some previous knowledge of the subject, for it frankly refers them to other textbooks for information as to the basic fundamentals. It begins with a brief description of some immunochemical aspects of allergy by Pringle followed by two chapters devoted in detail to methods of diagnosis. Then follows a rather brief description of the clinical aspects of nasal and bronchial allergy, with many more pages being devoted to hyposensitization procedures, constitutional reactions, status asthmaticus, aerosol therapy, bronchoscopy and an especially good section to useful drugs. Drug allergy, written by Credille, is next considered as well as food and gastrointestinal allergy. A considerable amount of space (62 pages) is devoted to allergic dermatoses, 35 being devoted to patch testing alone. While this is unusual for a small manual devoted to clinical allergy, it should be appreciated both by allergists and dermatologists. There is likewise a rather large chapter on pollen identification (61 pages) by Durham and McKay and one by Christensen and Swaebly on fungus and mold identification (17 pages) which should prove invaluable to allergists utilizing these procedures. Likewise additional space has been given to discussion of the endocrine and vascular aspects of allergy, pulmonary function and collagen diseases, because of the allergists' recent interest in these subjects. There is a good appendix devoted to the preparation of extracts and to pollen and mold testing. An unusual feature is a chapter on office planning for the care of allergy patients. Despite its multiple authorship, the text is easily readable and with a few minor exceptions, the opinions expressed represent those of allergists in general. Because of the special features already mentioned, it is recommended for use not so much for the general practitioner or medical student as for the beginner in allergy or postgraduate student, as well as the practicing allergist.

L. T.

HUMAN FACTORS IN AIR TRANSPORTATION. OCCUPATIONAL HEALTH AND SAFETY. By ROSS A. MCFARLAND, PH.D., Associate Professor of Industrial Hygiene, Harvard Univ. School of Public Health. Pp. 830; illustrated. New York: McGraw Hill Book Co., 1953. Price, $13.00.

THIS is a very timely and important book. It deals with problems of aviation medicine, a field of rapidly developing scope and importance, which has been heretofore discussed largely from the standpoint of military medicine. The emphasis of this volume lies on civilian aspects. There are sections on The Nature and Extent of Airline Operations, Se-

lection and Training of Personnel, The Maintenance of Health and Efficiency of Flight Personnel, The Selection, Placement and Health of Ground Personnel, Safety on the Ground and in Flight, Sanitation and Health in Airline Operations, Passenger and Service Problems, and Health and Medical Services in Air Transportation. The author brings to his task special training and long interest and experience in the field, including such assignments as membership of the International High Altitude Expedition to Chile in 1935, Medical Coordinator of the Pan American World Airways System, Operations Analyst for the 13th Air Force in the Solomon Islands Campaign, and other equally significant assignments. The book is well written and documented and should prove a highly acceptable text in aviation medicine. R. K.

ENDOCRINE TREATMENT IN GENERAL PRACTICE. Edited by MAX A. GOLDZIEHER, M.D., and JOSEPH W. GOLDZIEHER, M.D. Pp. 474; 19 ills. New York: Springer Publishing Co., 1953. Price, $8.00.

TWENTY-ONE authors have contributed to this book. As is so often the case in such books, some sections are better than others. The editors wrote the chapter on Obesity and Leanness. They continue to recommend thyroid, pitressin tannate in oil and posterior pituitary powder in the treatment of obesity. Similar inaccuracies dot their work. Other chapters are very well done. W. P.

THE ESSENTIALS OF MEDICAL DIAGNOSIS. BY RT. HON. LORD HORDER, G.C.V.O., M.D., F.R.C.P. (LOND.) and A. E. GOW, M.D., F.R.C.P. (LOND.). 2nd ed., revised with assistance of RONALD BODLEY SCOTT, M.A., D.M., F.R.C.P. Pp. 462; 50 ills., 6 in color. Baltimore: Williams & Wilkins Co., 1953. Price, $6.00.

THIS book is a refreshing piece of work among the many usual books on the subject of Medical Diagnosis. The reviewer feels it is particularly aimed for the medical student although the authors include also practitioners of medicine. Physical diagnosis is the main theme. The approach is such that data is assembled in such a way that the mental processes which the observer or examiner goes through is enfolded as the examination proceeds.

The patient is evaluated and examined according to the various systems of the body rather than in the usual way of examination from head to foot without specific consideration for systemic function. Brief but pertinent and concise information is offered concerning anatomical, physiological and normal valuations of the various systems as an examination is being made.

The reviewer feels that this book should be an essential part of the library of the student as well as the practitioner of medicine.

G. M.

THE CONTROL OF COMMUNICABLE DISEASES. BY HUGH PAUL, M.D., D.P.H., Medical Officer of Health, Smethwick County Borough, with a Foreward by G. S. WILSON, M.D., F.R.C.P., D.P.H., Director of the Public Health Laboratory Service. Pp. 526. London: Harvey and Blythe Ltd., 1952. Distributed in U.S.A. by John deGraff, Inc., New York. Price, $9.50.

THE author has attempted not only to assess the requirements of medical students and general practitioners but has attempted to make this book useful to health officers as well. The task of dealing with individual diseases which are endemic or epidemic in communities is described in detail; likewise the general principles of epidemiology which should be the ever present equipment alike of the specialist and the general practitioner. Perhaps the outstanding feature of this book is the courageous manner in which the author has attacked the habit of adopting conventional methods, in spite of corrections and modifications which advancing scientific knowledge has shown to be necessary. The chapters on immunization against smallpox, on measles and on the common cold may please some and infuriate others, but the author, in giving both conventional and controversial points of view, is careful to state the arguments on both sides. Statistical illustrations are generously quoted and are up-to-date; their significance in relation to each problem is discussed. J. K.

PAIN SENSATIONS AND REACTIONS. BY JAMES D. HARDY, PH.D., Assoc. Prof. of Physiology, HAROLD G. WOLFF, M.D., Prof. of Medicine (Neurology), and HELEN GOODELL, B.S., Research Fellow in Med.; all at Cornell University Medical College. Pp. 392; 130 ills. Baltimore: Williams & Wilkins Co., 1952. Price, $6.50.

HERE is a volume which should be in the library of every physician. This is especially true since pain is such a universal complaint encountered by all who practice medicine.

The wealth of material included here, much of it the result of original work by the authors, may serve as a point of departure of further investigation by others. The over five hundred references in the bibliography are very valuable. The discussion includes an historical portion on the earlier concepts of pain, together with a presentation of the authors' techniques for investigating sensation, and their formulation of what the pain experience is. Theirs is a very broad concept, which, of course, is as it should be, involving as it does, all parts of the organism, the psychologic and emotional, as well as the physical. The book is well written, practical and decidedly worthwhile. S. G.

THE PHARMACOLOGY OF ANESTHETIC DRUGS. By JOHN ADRIANI, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans. 3rd ed. Pp. 179; 155 ills. Springfield, Ill: Charles C Thomas, 1952. Price, $9.50.

DR. ADRIANI has done a marvelous job of revising the third edition of this textbook. He has edited in one volume brief but accurate information concerning not only the pharmacological activities of anesthetic drugs but also the physical and chemical properties of these drugs.

This text is prepared as an outline with many diagrams and data in tabular form. This technique of presentation makes this book very valuable as a reference book and as an outline for a thorough review of the pharmacological properties of all the drugs used by anesthesiologists.

Dr. Adriani should be congratulated on the thoroughness with which he has presented one of the most important basic subjects in anesthesiology.

This textbook should be included in the libraries of all anesthesiologists. L. K.

THE PRINCIPLES OF NEUROLOGICAL SURGERY. By LOYAL DAVIS, M.D. 4th ed. Pp. 544; 354 ills., 4 in color. Philadelphia: Lea & Febiger, 1953. Price, $8.50.

IT is a pleasure to review this book. In this and the previous editions the reader finds provided an excellent short account of diagnosis and treatment of the usual neurosurgical conditions. Emphasis is placed on diagnosis and the general principles of treatment without cluttering the script with unnecessary details. An admirable and much needed chapter on peripheral nerve injuries and how they should be handled replaces the previous curt summary on this subject. Many new and excellent illustrations are provided and the whole form and texture of this edition is a vast improvement over the earlier issues.

F. G.

ATLAS OF MEDICAL MYCOLOGY. By EMMA S. MOSS, M.D., and ALBERT L. MCQUOWN, M.D., Pathologists, Charity Hospital of Louisiana and Louisiana State University School of Medicine. Pp. 245; 247 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $8.00.

THE value of a new book is judged in the light of what is already available. The clinical and laboratory features of medical mycology have enjoyed a unique position in that they have been excellently and repeatedly recorded by Conant and associates at Duke University, and by several others. Nevertheless, this reviewer finds in Moss and McQuown's Atlas a definite contribution to laboratory diagnosis of the mycoses. As the title implies, the presentation is predominantly illustrative, the synoptic text material serving primarily as framework for photographs. The effect is surprisingly good because the authors obviously know their subject well and they have obtained many first-rate, original illustrations. It is difficult to find a serious omission or error, but one can suggest inclusion of differential diagnosis in future editions.

E. S.

PRACTICAL BLOOD GROUPING METHODS. A MANUAL OF IMMUNOHEMATOLOGY. By ROBERT L. WALL, M.D., Dept. of Research Medicine, Ohio State University Hospital, Columbus. Pp. 175. Springfield, Ill.: Charles C. Thomas, 1952. Price, $5.00.

THIS is a brief discussion of the human blood groups and the methods for their detection. The techniques of the various tests are adequately detailed, and the proper interpretation of results is considered for each test. The most common causes of false positive and of false negative reactions are indicated. The author rightly emphasizes the inherent variability in certain procedures, for example, in the Coomb's test great differences are often encountered in the titers of different lots of anti-human globulin serum.

The author's style is concise and lucid, and his approach objective throughout. This volume is recommended to physicians who wish to review the important advances in immunohematology and their practical applica-

tion. Clinical pathologists, medical students and medical technicians will also find much useful and valuable information in this work.

C. Z.

THE LIVING BRAIN. By W. GREY WALTER, M.A. Sc.D. (Cantab.). Pp. 311; 23 ills. New York: W. W. Norton & Co., 1953. Price, $3.95.

THIS book is an attempt to familiarize the general public with electroencephalography, its history, its clinical use for the diagnosis and localization of cerebral disorders as well as with possible theoretical and philosophical applications. Electric models of nerves, of elementary reflex behavior and of conditioned reflexes are presented. It is shown to what amazing extent higher cerebral functions, such as learning, can be imitated by electronic models. How far electrical circuits will help us to obtain a deeper insight into the processes of memory, sleep, fatigue, hypnotism, or psychopathologic phenomena remains to be seen. But whether one is inclined to accept far-reaching conclusions at the present stage of our knowledge or not, one has to admit that the author has an extraordinary gift of being able to fascinate the reader and to present a rather complex subject with great clarity. The book is highly recommended to anybody wishing to acquaint himself with recent developments in this branch of neurophysiology.

E. S.

MEDICINE. Two volumes. Edited by HUGH G. GARLAND, M.D., Physician in Charge, Department of Neurology, General Infirmary at Leeds, and WILLIAM PHILLIPS, M.D., Senior Physician and Physician in Charge of Cardiac Department, Cardiff Royal Infirmary. Pp. 2146; 248 ills., 7 in color. New York: St. Martin's Press, Inc., 1953. Price, $25.00.

THIS is an important new publication in the field of Internal Medicine. It has long been recognized that a textbook in medicine, in order to be well-balanced and authoritative, must be the product of multiple authors. The more numerous the authors, the greater is the task of the editor to avoid duplications and improper emphasis; the fewer the authors, the greater is the editor's task to insure adequate coverage. The 40 contributors to this text have produced a very excellent treatise, reasonably well-balanced.

The arrangement of material in most English language textbooks of medicine has followed a rather stereotyped outline devoted to chapters on specific diseases by etiology or system involved. The continental writers have, for years, followed a better plan, by beginning with consideration of the patient as a whole. This work very laudably devotes its opening chapters to such subjects as The Evolution of Modern Medicine; The Assessment and Promotion of Physical Health; Of Mental Health; The Natural History of Disease; The Social Aspects of the Etiology of Disease; and the Genetic Factor in Disease; The Patient as a Person; Nutrition and Disease; Infection and Immunity; Neoplasms; Principles of Diagnosis; Principles of Treatment; and Rehabilitation.

The third distinctive feature is the presentation of the material in two volumes. Half a century ago, the most popular textbooks in the world were the two-volume works by Strümpell and by Dieulafoy. Yet English writers have continued to restrict their texts to single volumes, either unwieldy because of their size or too short to give the student adequate coverage. The reception of this work in academic circles will, therefore, be watched with interest.

There are fairly numerous illustrations, well selected and well reproduced. The chief shortcoming from the standpoint of content is the wholly inadequate coverage of allergic conditions, covering as they do scarcely a dozen of the 2146 pages.

R. K.

DERMATOLOGY IN GENERAL PRACTICE. By JACOB HYAMS SWARTZ, M.D., Assistant Professor of Dermatology, Harvard Medical School and Post-graduate School. Pp. 581; 253 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $11.00.

Dermatology in General Practice represents a 581-page replacement for Swartz's Diagnosis and Treatment of Skin Diseases. The book contains many good items, among which are excellent illustrations both clinical and histological; chapters on the care of normal as well as abnormal skin; differential diagnosis tables; and a detailed section on mycotic infections, a subject in which the author is an acknowledged expert. While the volume has much valuable material, the arrangement of its presentation leaves much to be desired. Essentially, the topographical approach is employed, but since most eruptions are not confined to a particular area, for example, scalp, face, trunk, extremities, and so forth, there seems to be no consistent connection between the heading of the section and the location of the lesion as illustrated; that is, there are photographs of diseased hands, breasts

and legs in the section of the book dealing principally with skin diseases of the face. Furthermore, the arbitrary topographic division makes certain portions of the presentation little more than an index. This mechanical defect should be overcome in future editions in order to make the commendable data more easily and logically accessible. H. B.

THE PSYCHIATRIST AND THE LAW. By WINFRED OVERHOLSER, M.D., Superintendent, St. Elizabeth's Hospital, Washington, D. C. Pp. 147. New York: Harcourt, Brace and Co., 1953. Price, $3.50.

THIS book is the presentation of four lectures on psychiatry and the law by the first winner of Isaac Ray Award of the American Psychiatric Association. The first chapter is an orientation to psychiatry while the second indicates areas of desirable co-operation between law and medicine. The third discusses the mentally sick patient and the law in relation to his disposition and treatment, while the fourth discusses the psychiatrist in the courtroom. The content of all four lectures is interesting, stimulating and challenging and highly recommended for informative reading. O. E.

POLIOMYELITIS. By W. RITCHIE RUSSELL, M. D., Consulting Neurologist to United Oxford Hospitals. Pp. 79; 29 ills. Baltimore: Williams & Wilkins Co., 1952. Price, $3.00.

THIS monograph on Poliomyelitis by one of England's best known neurologists is an excellent one and is recommended for all who have any interest whatsoever in the disease. It is particularly noteworthy to the reviewer because it is written by a neurologist and as a result is not full of the inaccuracies which are so often found in the articles discussing this disease. The attitude toward the treatment including the "Kenny treatment" is refreshing and sensible, as one would expect. The emphasis on immediate cessation of activities, as soon as the diagnosis is suspected, as well as the discussion of the conservative stage are particularly praiseworthy. S. G.

NEW BOOKS

Gastric Cancer. By ALFRED H. IASON, M.D.; Surgeon, Manhattan General Hospital; Instructor in Anatomy, New York Medical College and Flower Hospital. Pp. 316; 100 ills., 5 tables. New York: Grune & Stratton, 1953. Price, $7.50.

THE stated purpose of this book is to summarize the existing literature on gastric cancer. Considerable attention, however, is also given to esophageal cancer and the chapters on anatomy and histology are broadened to include the small and large intestine. There is a commendable attempt to present the data in an orderly fashion but the effort is weakened by repetition of some phases of the subject under different headings. The pertinent observations and reports which have appeared in the literature are drawn on freely and for the most part uncritically. Failure to weight some of the material in terms of importance is probably responsible for some unintentional but nevertheless erroneous impressions. For example, in the chapter dealing with the complications that may develop after surgery, the misleading impression is conveyed that anastomotic ulcer appears in 5% of the cases in which gastrojejunostomy is performed for cancer of the stomach.

In a field already distinguished by outstanding contributions, this book that admittedly adds nothing new, cannot be said to be an especially meritorious review of what is already known. J. B.

Problems of Aging. Transactions of the 14th Conference, September 7-8, 1951. Edited by NATHAN W. SHOCK. Pp. 138; 9 ills. New York: Josiah Macy, Jr. Foundation, 1952. Price, $3.00.

A stenographic record of an informal discussion by 28 authorities in a wide range of medical fields and a particular interest in the problem of old age, and also representatives of cognate social and scientific disciplines. It makes excellent reading. R. K.

Medical Clinics of North America. New York Number, Vol. 36, No. 3, May, 1952. Pp. 306; 37 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00 per annum.

THE contributors are all from New York City and have produced a symposium on endocrine and metabolic disorders that should be of unusual interest. Particular attention is given to the use of anti-thyroid drugs, radioactive iodine in thyrotoxicosis, thyroid tumors, the hormonal treatment of certain neoplasms, insulin allergy, diabetic coma, ACTH and cortisone, electrolyte and water metabolism, osteoporosis, hypercholesteremia and tetany. R. K.

British Encyclopaedia of Medical Practice including Medicine, Surgery, Obstetrics, Gynaecology and Other Special Subjects. Medical Progress, 1952. Editor-in-Chief, THE LORD HORDER, G.C.V.O., M.D., F.R.C.P., Consulting Physician to St. Bartholomew's Hospital, London, England. Pp. 339. London: Butterworth & Co., 1952. 1952.

British Encyclopaedia of Medical Practice including Medicine, Surgery, Obstetrics, Gynaecology and Other Special Subjects. Cumulative Supplement of the First Edition, 1952. Editor-in-Chief, THE LORD HORDER, G.C.V.O., M.D., F.R.C.P., Consulting Physician to St. Bartholomew's Hospital, London, England. Pp. 451. London: Butterworth & Co., 1952.

Recent Advances in Nutrition Research with Emphasis on the Newer B Vitamins. Proceedings of the Scientific Sessions of the Seventh Annual Meeting, The National Vitamin Foundation, Inc., New York, April 3, 1952. Pp. 129; 17 ills. New York: National Vitamin Foundation, Inc., 1952. Price, $1.50.

Technion Yearbook, 1950. Pp. 352; illustrated. New York: American Technion Society, 1952.

Technion Yearbook, 1951. Pp. 360; illustrated. New York: American Technion Society, 1952.

Problems of Life. An Evaluation of Modern Biological Thought. By LUDWIG VON BERTALANFFY, University of Ottawa, Ottawa, Canada. Pp. 216. New York: John Wiley & Sons, Inc., 1952. Price, $4.00.

The Moral Theory of Behavior. By FRANK R. BARTA, M.D., F.A.C.P. Pp. 35; 3 ills. Springfield, Illinois: Charles C Thomas, 1952. Price, $2.00.

THE theory of this lecture given by the Director of the Department of Psychiatry and Neurology of Creighton University School of Medicine is based on Thomistic and Aristotelian principles of normal behavior, including a mixture of philosophy, psychology, religion, and a few psychiatric terms. The content is highly personal, very complicated and does not seem to clarify, or be a new answer to what the author terms "the enigma of mental illness." O. E.

Kitchen Strategy. By LEONA M. BAYER, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, and EDITH GREEN, Television Cooking Expert, San Francisco. Pp. 112, 10 ills. Springfield, Illinois: Charles C Thomas, 1952. Price, $3.75.

THIS book should prove a worth while kitchen guide to the housewife and mother who wishes to give her family the best in nutritional foods, so essential to good health. Because of its detailed information on dietetic management in minor illnesses, it can also be a time saver to the physician when advice as to diet becomes necessary. M. H.

Dynamic Psychiatry: Frustrated Women, Volume 3. By LOUIS S. LONDON, M.D. Pp. 132. New York: Corinthian Publication, Inc., 1952. Price, $3.00.

THIS book of case histories covers four different areas of psychiatric manifestations: hysteria and anxiety neuroses, psychosomatic illness, obsessional and compulsory thinking, and sexual deviations in the female. The case material deals almost exclusively with sexual fantasy, sexual activity, and sexual emotions. Other components of the personality are ignored. Dreams are interpreted without the patient's associations. While the case presentations have their interest the content might easily lead the reader to assume that only the sexual components of a patient's life need be dealt with in attempting to cure a neurosis or psychosomatic illness. O. E.

The Mechanisms of Disease: A Study of the Autonomic Nervous System, the Endocrine System and the Electrolytes, in their Relationship to Clinical Medicine. By JOSEPH STAMBUL, M.D., Chief, Cardiovascular Department, Albert Einstein Medical Center (Eastern Division). Pp. 746. New York: Froben Press, Inc., 1952. Price, $15.00.

IN this volume, one finds the author attempting to correlate data, much of which has been collected from the older literature, dealing with the actions of the autonomic nervous system, hormones, and electrolytes upon cellular physiology. It is noteworthy that in his biblography, covering 42 pages, there appears only a handful of references later than 1940. Much of the material presented is not in keeping with current thinking but reflects older viewpoints; for example, " a diuretic must be a substance that mobilizes sodium chloride from the edematous tissues to the circulation." In his discussion on the intermediary metabolism of fat, none of the important contributions of the past 5 years has been mentioned. Although the book may have some historical interest, the reviewer is unable to recommend it. C. S.

Second Report Alcoholism Subcommittee. World Health Organization Technical Report Series No. 48. Pp. 39. Geneva: World Health Organization, 1952. (Columbia University Press, Agents for United States). Price, $.25.

A concise summary of current knowledge of alcoholism, including evaluation of current methods of treatment.

Headaches: Their Nature and Treatment. By STEWART WOLF, M.D., Prof. and Head of Dept. of Medicine, University of Oklahoma, and HAROLD G. WOLFF, M.D., Prof. of Medicine (Neurology), Cornell University. Pp. 177; 7 ills. Boston: Little, Brown & Co., 1953. Price, $2.50.

THESE two authors, pioneers in psychosomatic research, have published their first book for the layman because they feel he should know of newer developments and trends in medicine. They present their theories as to the causes of headache. Headaches due to organic disease and to migraine are discussed. A chapter is devoted to muscular tensions in the head and there is a full discussion of "sinus headaches."

Illustrations, case histories and the pyschological factors in headache are dealt with in an able manner. Although written primarily for the layman this book is highly recommended for physicians also. It should help in initiating and carrying out treatment in this common, but difficult, syndrome so often met in daily practice. O. E.